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Functional Restoration for the Stroke Survivor: Informing the Efforts of Engineers

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Abstract

As bioengineers begin to notice the importance of therapy in the recovery from stroke and other brain injuries, new technologies will be increasingly conceived, adapted, and designed to improve the patient's road to recovery. What is clear from engineering history, however, is that the best engineering efforts are often built on strong scientific foundations. In an effort to inform engineers with the necessary background on cutting edge research in the field of stroke and motor recovery, this article summarizes the views of several experts in the field as a result of a workshop held in 2006 on the topic. Here we elaborate on several areas relevant to this goal, including the pathophysiology of stroke and stroke recovery, the biomechanics, the secondary peripheral changes in muscle and other tissue, and the results of neuroimaging studies. One conclusion is that the current state of knowledge is now ripe for research using machines but that highly sophisticated robotic devices may not yet be needed. Instead, what may be needed is basic evidence that shows a difference in one therapeutic strategy over another.

Keywords

CVA; control; movement; muscle; rehabilitation human; stroke

There has been considerable attention in recent years to the natural course of recovery from stroke and to the effects of therapeutic intervention. This should not come as a great surprise, because stroke is by far the leading cause of physical disability among adults in the United States, with annual rehabilitation costs in the billions. The prevalence of stroke is enormous. According to the American Heart Association, the number of stroke survivors increased from 1.5 million in the early 1970s to 2.4 million by the early 1990s,¹ to over 3 million today. This increase goes hand in hand with the aging of our population. Currently, the population of those 65 years or older is approximately 33+ million (12.7% of US population in 1999) and is projected to be 53 million by 2020 and 77 million by 2040 (see www.strokeassociation.org). The percentage of Americans 45–54 years old living with stroke is under 2%; it is almost 4% in those 55–64 years old, rises to 6% for those 65–74, and rises to more than 10% for those 75 and over.² Clearly, the issues related to the long-term treatment of stroke will be increasingly important societal issues.

Furthermore, although the incidence of stroke is falling overall, presumably because of the improvement in medical management of hypertension, hyperlipidemia, and vascular disease,

the prevalence is rising, thereby increasing the importance of long-term management requiring aggressive therapeutic, rehabilitative, and social efforts for the nation as a whole. More than 700,000 people in the United States suffer a stroke each year.³ Of these, 60%–75% will live at least 1 year longer, resulting in a stroke survivor population of 2–3 million.^{3,4} Acute motor weakness persists in more than 40% of the cases, leading to a huge cohort of people with chronic hemiparesis.^{5–7} Furthermore, the United States spends \$30 billion a year on physical rehabilitation; the largest subgroup of this population (30%) consists of stroke survivors. Approximately 3.5 million stroke survivors are discharged per year in the United States, and up to 70% of the associated rehabilitation costs come from labor.

Scientists and engineers have recently focused on technology as a means of speeding recovery, enhancing treatment, quantifying progress, and improving our understanding of the mechanisms of disease. However, there are several issues in the application of technology to stroke rehabilitation that need to be considered and carefully debated by scientists, clinicians, and bioengineers as they collaborate to enhance rehabilitation.

In stroke lesion models, the effects of robotic interventions are far less robust than what might be expected, and clinical trials of robotic interventions in human stroke rehabilitation have been similarly disappointing. The yield results for these trials are less than vigorous, as they identify statistically significant gains that have little clinical meaning or relationship to functional effectiveness. So, although some mythology has evolved around the use of automated techniques, such as body weight–supported treadmill training, constraint-induced therapy, robotics, virtual reality, stimulation, and motor imagery, the few blinded controlled clinical trials show only a modest improvement in physiologic measures that do not translate to improvement in function. Furthermore, there is a relative paucity of such carefully controlled trials, which leads to a disproportionate ratio of mythology to data.

In addition, in meeting after meeting about robotic interventions, one hears about innovative engineering ideas for robotic devices and the ways in which they are combined with other complex interventions, such as virtual reality, brain–computer interfaces, imagery, and bimanual as opposed to unilateral activities. However, clinicians and neuroscientists are not in agreement on how to tell engineers what they want robotic machines to do. Researchers also do not conclusively know whether any one of these approaches is useful. They nevertheless accept the utility of adopting two or three approaches, as if more were better.

A key presumption underlying stroke treatment is that neuroplasticity is responsible for recovery following stroke and the plastic changes in the structure and operations of relevant brain circuits are induced primarily by rehabilitation. Not yet known, however, are the ideal patterns of rehabilitation or the best technological measures of improvement. A number of such measures have been proposed for this purpose; thus far, none have been demonstrated to provide the optimal parameters of training. Electromyographic (EMG) timing and amplitude during reaching and walking, changes in functional magnetic resonance imaging (fMRI), and transcranial magnetic stimulation (TMS) have been used in place of measurable behavioral gains as if they were outcome measures that had value within them or had meaning outside of the behaviors with which they were meant to be correlated.

Another issue is models of biomechanics of movement. The conceptual framework for the recovery of locomotion, which is derived primarily from animal models and supported by studies in humans, relies on a pattern of sensory inflow that can promote rhythmical activity in the spinal centers. Although that model does not account for such factors as posture and balance in humans, it offers a validated approach for rehabilitation of the lower extremities, at least in terms of the rhythmical aspect of locomotion. However, there is no such model for the upper extremity.

Finally, confounding conceptual issues associated with stroke rehabilitation is the misuse of interpretations of models of training and of neural repair. Terms such as activity-dependent plasticity, constraint-induced therapies, and rules of locomotion are used in a somewhat cavalier fashion, as if they were proven concepts and schemas that deserve a scientific stamp of approval. In some ways, researchers have been developing a belief system that may not yet be warranted, one that attempts to drive plasticity through the optimal application of sensory drives for learning motor skills, for intensifying practice, for improving outcomes, or for limiting the errors patients make when they are trying to walk or move or use language. There is little available in the form of clear conceptual constructs that might guide translational neuroscience and practical applications of stroke rehabilitation, one that defines the tasks that should be practiced, develops response curves for enabling that practice, and maximizes the acquisition of skills.

To improve outcomes of stroke rehabilitation, engineers and developers need a better understanding of several components of the recovery process: changes that occur as the result of recovery, how rehabilitation and training affect those changes, and how to measure them. We need to uncover the pathophysiology of recovery and the ways in which interventions may be optimized to affect it.

Consequently, rather than invite a group of roboticists to present their work, the State of the Science Workshop on Functional Restoration for the Stroke Survivor: Informing the Efforts of Engineers invited an expert panel of neurophysiologists and clinician researchers to a 2-day workshop with the goal of preparing a summary of current knowledge in the area of understanding and testing stroke rehabilitation strategies. As an interactive meeting, many of the topical issues were comprehensively debated, resulting in consensus on several key points. This article explores the debates related to whether rehabilitation might be enhanced by a better understanding of the measures of treatment effects; the physiology and pathophysiology of plasticity; whether error reduction or amplification facilitates recovery; the mechanisms of motor relearning; the mechanisms of muscle adaptation; the biomechanics of movement; the relationship to neuroimaging; the role of biological markers; and the decisions of who, when, and how long to treat. What was clear from this conference is that technologically driven rehabilitation of the stroke survivor is an area whose time has definitely come, and there are several solution pathways, discussed in the sections below.

State of Rehabilitation and the Importance of Technology

Studies that track changes in Fugl-Meyer scores from the acute through late care of stroke patients consistently show that individuals with moderate deficits make the most gains early on. However, all patients, whether they have low, moderate, or high levels of functional impairment at the outset, reach a plateau within the first 200 days of stroke following robotic intervention. The Barthel Index for patients with stroke shows the same pattern.

Researchers and clinicians would like to believe that impairment and function reflect one another and are correlated, that targeting impairment will improve function, and that improved function will increase a person's degree of participation in society. However, these relationships are not as clearly established as one might prefer. For instance, a total of 800 patients with stroke have been evaluated in randomized, controlled, blinded, clinical trials after treadmill training with weight support.⁸ Outcomes for these patients were no better than they were for patients who did not have treadmill training. Four upper extremity robotic training studies used the Fugl-Meyer upper extremity scale,⁹⁻¹² and all showed a small degree of improvement after robotic rehabilitation therapy. Fugl-Meyer scores rose from less than 20 immediately after stroke to around 35 within 200 days afterward. There was no further

improvement in Motor Status Scale score, however. The improvements are modest and may not be distinguishable from conventional therapy, which is also often modest and variable.

In fact, rehabilitation of the upper extremity following stroke has not been highly effective for a variety of reasons, not the least of which is because it typically begins late in the treatment process. Patients routinely are ambulated first, and, as result, the upper limb is often neglected in early rehabilitation. The few studies that have been done with robotics have provided at least some indication of improvement in movement of the shoulder and elbow.¹³ Even the studies that suggested there were improvements in strength or range of motion in the shoulder have not, however, demonstrated functional change that was clinically significant. There is also the sense that wherever there has been some evidence for improvement following rehabilitation, it has been found in patients who have a considerable amount of motor control to begin with, not in patients who are highly impaired and have just a few synergies.

Evidence-based medicine

The Physiotherapy Evidence Database (PEDro) scale, which was developed in Australia and is used worldwide to classify the quality of the evidence produced in clinical studies, assigns levels of evidence based on a set of 10 study design criteria.¹⁴ The highest level, 1a, is assigned when clinical studies meet six or more of these criteria.

Nine studies conducted on robotic rehabilitation of the upper extremity between 1999 and 2005 have been included in the PEDro database, and five have a PEDro score of 6 or better. In comparison, only 5 of 10 studies of neurodevelopmental therapy (NDT) had a PEDro score of 6 or better.¹³ Of 10 studies of additional enhanced therapy, 7 had a PEDro score of 6 or better. There have been 14 randomized controlled clinical trials of constraint therapy, and 5 had a fair to excellent PEDro rating. A high number of studies of robotic therapy, therefore, are meeting stringent study design criteria.

The improvement shown in these studies tends to be restricted to the shoulder and elbow. Five of the nine studies of robotic therapy demonstrated improvement in motor status or power or both in the shoulder and elbow. There was no effect on wrist or hand movement in two of these studies. In addition, there was no difference in motor function and power when interactive robotic arm training was compared with acute and continuous passive motion.

Moreover, most of the outcome measures in studies on rehabilitation therapy have focused on impairment level not function. The Canadian Stroke Network (CSN) has concluded that study findings concerning five areas of stroke rehabilitation have been negative or limited.¹³ The CSN noted that NDT and EMS/biofeedback have not been superior to other approaches and that there is uncertainty about the effect on function from enhanced therapy, repetitive task-specific training, and sensorimotor training.

In contrast, the CSN has reported that sensorimotor training with robotic devices does improve functional and motor outcomes of the shoulder and elbow but not of the wrist and hand. It acknowledges that preliminary evidence suggests that virtual reality combined with real-world therapy improves functional and motor outcomes. The CSN also considers constraint-induced movement therapy to be of benefit to patients who have some active wrist and hand movement, and it notes that functional electrical stimulation therapy improves function of the upper extremity.

The CSN nevertheless has concluded that most of the approaches or techniques for upper extremity rehabilitation are successful or positive only for patients who already show some signs of recovery. So the initial degree of motor impairment is the best predictor of motor recovery. In a study by Nakayama,⁷ for example, 14% of patients who had little or no active

movement on admission achieved complete motor recovery and 30% had partial recovery. Similarly, in a study by Kwakkel,¹⁵ 11.6% of patients who were severely impaired on admission had a complete recovery after 6 months of therapy and 38% had partial recovery.

Although functional recovery goals are appropriate for patients who are expected to achieve a greater amount of motor recovery of the arm and hand, compensatory treatment goals should be pursued for patients whose recovery outcome is expected to be poor, such as those with visual field deficits, cognitive deficits, hemispatial neglect, or visual inattention.

Robotics appears to be able to improve the quality and effectiveness of therapy if the dosage is known and if the intervention is done at the right time for the right patients.¹³ However, the benefits are highly joint specific, and they do not generalize to show improvement in the functional level of the patient.

Rehabilitation of the lower limbs

There are many aspects of impairment that must be considered when thinking about how to augment therapy with robotics. What should the devices target in terms of locomotor impairment? Is there a specific type of patient who would benefit from the sequencing of manual versus robotic interventions? Are there benefits to robotic devices that have not yet been realized, such as measurement capabilities that may be used to monitor patient progress in a quantitative manner? Are there ways to modify the entire environment to achieve specific training goals? Is the reason for using a robot just to replace therapists to reduce the cost of rehabilitation? Or can robots do something better than a therapist can do or do things that a therapist can't do? Is retraining a central pattern generator using a treadmill really the core issue in lower extremity rehabilitation? Some would argue that the cortex is central for bipedal locomotion; because humans are unstable, they need much more than the spinal cord to have any type of bipedal locomotion. They need the cortex and the vestibular and brain stem systems. Is treadmill locomotion fundamentally different from overground locomotion because of the differences in propulsion? If so, why are patients trained on treadmills when there may be limited transfer to overground stepping? What is the relationship of complexity to efficacy for robotic gait training?

The Lokomat Robotic device (Hocoma, Zurich) has been designed to produce a fundamental gait pattern, which would be effective if the objective was simply to get patients up and moving their legs.¹⁶ However, spinal cord locomotor control is highly complex. The spinal cord listens to many sources of sensory input. So a more sophisticated robotic device may, for example, control the pelvis in five degrees of freedom, assist only as needed by touching flexor and extensor surfaces of the skin at certain times, and adapt to the ability to be compliant. Producing a more naturalistic movement may produce improved clinical outcomes.

The importance of central pattern generator

The central pattern generator was discovered by investigators who found that inner neurons could oscillate independently of afferent and supraspinal input and afferent neurons in the presence of excitation, either pharmaceutically or electrically induced. In humans, the stimulation of the inter-neurons at a constant rate produces oscillatory movement.

Unfortunately, the concept of the central pattern generator remains underspecified and is not understood even at a basic level. What is important to comprehend is that walking is the interaction of supraspinal and afferent input with the spinal interneurons. What needs to be determined is how this interaction after injury can promote the recovery of walking.

In the complete human spinal cord (the human spinal cord that has been functionally isolated from the brain), there is an intrinsic flexor-extensor control at the level of the spinal cord. The

patterns across the levels of the spinal cord are coordinated. Changing loading conditions or velocity will influence the afferent information that enters the spinal cord and therefore change the response. So by changing the velocity of stepping, which changes the rate of entry of all the afferent information, a chronic pattern can be made more functional. The same phenomenon occurs with loading. When the two are manipulated together, there is an interactive effect. So there is an ensemble of afferent information that helps to guide patterns. A working model of walking involves the interaction of the properties of inter- neurons that have defined connections across the spinal cord. There are interactions among the interneurons as well as with sensory information, cutaneous loading, and stretch, and all of the interactions come together in order to generate the walking pattern.

The process of walking

An underlying problem, however, is an overall lack of understanding of the principles involved in walking, in terms of defining and quantitatively assessing major impairment.

Walking, therefore, may be defined with respect to some of the integral subtasks that reflect the performance of underlying neurological systems that are functionally important to the task and that could be differentially impaired. If clinicians could be more quantitative and specific about what is broken, they would be able to determine whether or not they were fixing it and whether or not a robotic device was addressing the specific issue that is the most important to a particular patient.

Quantitative assessments that allowed clinicians to discriminate among patients of varying abilities might demonstrate a strong correlation with clinical judgment of important tasks, like balance control or the generation of appropriate stepping. Such assessments might be used to compare performance between patients and between sessions for individual patients and to evaluate the mechanics underlying the walking task. For instance, measurement of a concept like generating propulsion in the walking task might be based on the forces that generate propulsion, such as the interior/posterior ground reaction forces. Merging subtasks into systems that reflect underlying nerve physiological substrate might allow therapists to target more specifically the particular needs of a patient and to monitor what is being affected, what is not being affected, and how engineers may be more efficient in their design of robotic devices.

Once clinicians reach a level of understanding about a complex multifactorial output like walking speed as well as the specific deficits that the patient has, then they would have a clear idea of the types of controllers for position versus impedance, the kinds of constraints to place on a pattern, the modes of settings, and the shifts from working on passive motion of the legs versus the integration of balance into the picture.

Physiology and Pathophysiology of Neural Plasticity

For robotics in rehabilitation, animal models are useful for helping to understand a defined biological problem or mechanism, but it is a big step to take what is seen in well-defined animal models that have their own specific purpose and apply it to what happens in human disease states where lesions are often larger or much less localized. When scientists make inferences about adaptations that are associated with activity-dependent plasticity in rehabilitation, they must realize that there is not a good fit yet between plasticity and outcome, whether it is defined by functional magnetic resonance imaging (fMRI), transcranial magnetic stimulation (TMS), microstimulation studies, or network functional studies. Researchers do not have an understanding of the relationships between what is seen in physiology and what is demonstrated in behavior. Plasticity and behavior most likely are related within the nervous system, but it is highly unlikely that there is any linear relationship between changes in plasticity and the presence or absence of recovery.

Plasticity within the neural system

Plasticity occurs at many different levels. What goes on among connected neurons that are neighbors, or the small ensembles that are tuned to certain kinds of kinematics or quirks or directional movements, or those that are related to nodes and a distributed network relative to movement, both for the cognition for movement and for the actual movement itself?

Experiments in animal models examining the role of plasticity in learning in the intact brain and relearning or recovery in the damaged brain have generally focused on a single type of behavior in one principal brain area: skilled reaching or skilled movement in the motor cortex. These experiments use an intracortical microstimulation model to evaluate the relationship between structural and functional change in the cortex following environmental exposure.

Studies using this model have shown that motor maps of cortical activity in animals that have been trained to perform a skilled movement task involving the wrist and digits reflect the effect of behavioral change on functional reorganization and that at least spatially synaptic structural change and functional change are co-localized in the form of motor map reorganization. Nevertheless, the biology of the brain does not change in the same order of magnitude that behavior does.

The plasticity profile in these studies is phasic: Changes in synapse number occur approximately 7 days after the onset of training, but changes in maps tend to take another 10 days to appear. Change in synaptic function occurs about the same time as the change in synapse numbers, but it disappears after 10 days. There is, therefore, a nonlinear relationship, both in terms of magnitude and time, between plasticity and behavior, which complicates the use of plasticity as a measure of recovery.

In addition to neural signals that drive plasticity in the cortex, such as acetylcholine, learning and motor experience affect synaptic and motor map plasticity. Synaptic changes and changes in motor map organization also depend on the behavioral demands associated with skill acquisition.

There is no direct experimental evidence that structural change is needed for permanent functional change to occur. However, there is convergent evidence that synaptogenesis is localized within brain map areas that reorganize, synaptogenesis precedes map reorganization, and manipulations that reduce synapse number also reduce map size. Antagonists or induced synaptic depression that cause a reduction in synapse number also reduce the size of the brain map.

Mapping in the diseased brain

In a rodent model of focal ischemia, motor function does improve over time. However, the behavioral profile is not the same as it is in animals with a healthy brain that are learning from scratch. Reacquisition of behavior, not surprisingly, depends on skill training. In animals that have undergone skill training, there is a restoration of function in the cortex and physiological recovery as well as synaptic recovery.

Just as it stimulates plasticity in the intact brain, acetylcholine plays a role in the restoration of function in the diseased brain. Depleting the cortex of acetylcholine impairs recovery. Animals that have no or only small amounts of acetylcholine have limited recovery (less than 20%) after 5 weeks of training, whereas animals with normal levels of acetylcholine achieve almost 60% recovery after 5 weeks of rehabilitation.¹⁷ Animals that have a lesion as well as a reduction in acetylcholine have a reduced map size, whereas animals that have a lesion and normal levels of acetylcholine show an increase in map area.

Dysfunction in the brain following infarction appears to be biphasic. Immediately after infarction, there is an area of brain tissue outside of the infarction itself that cannot evoke movement. There is also a dysfunction that extends into intact cortex. One of the first effects of rehabilitation is a functional restoration as brain tissue becomes active. The second phase is reorganization as the brain compensates in response to the rehabilitation.

Plasticity is different in the initial acquisition phase and in the maintenance phase following rehabilitation. Researchers have hypothesized that the first stage of rehabilitation is resuscitation, and its effect is to restore health to the tissue outside of the infarction site. The second phase, or reorganization period, stimulates areas of the brain that are healthy enough to contribute to compensation. Map plasticity during recovery differs from the plasticity seen in initial learning. In response to rehabilitation, animals fall into a behavioral performance relapse or a transient expansion of dysfunction.

A number of experiments from several laboratories have shown that the type of plasticity depends on the area of the brain and the motor experience of the animal or the person. In the motor cortex, skill training induces synaptogenesis and map reorganization whereas endurance training in the motor cortex does not. The relationship among motor learning, motor adaptation, and plasticity depends on the type of experience, the area of the brain involved, and the type of plasticity that is being measured.

So, while understanding plasticity in the intact brain is useful, it is limited. The goal for basic scientists is not to describe the details of the rehabilitation that clinicians should be performing, but rather to identify the principles that drive plasticity and use them to guide translational research that will determine how to promote and optimize recovery.

Studying plasticity in the intact brain also fails to account for the fact that the neural architecture within the brain is quite different after a stroke. Determining the characteristics of each patient is just as important as identifying the principles of plasticity, because plasticity will be an interaction between the nature, intensity, duration, and salience of the rehabilitation treatment that is given in the neural environment, which is determined by age, time, lesion size, and lesion location.

The way to approach plasticity in the damaged brain is to start thinking about an interaction between a new neural environment, which is patient-specific, and the factors that foster plasticity.

Motor Learning

Most clinicians and researchers assume that one critical mode of recovery for a stroke survivor is the *relearning* of descending motor signals – signals that must be appropriate for a new nervous system of altered or lost neural resources and pathways. Learning in the nervous system involves not only a change in magnitude or a change in the number of synapses or the weight of the synapse or the size of the map but also a change in the patterns of neuronal firing and the functional connectivity. Cells often increase and decrease in activity, with no clear evidence of a consistent change. Firing also changes over time. Although the mean rate of firing over the entire time window is approximately the same, there is an early phasic burst that can take place in the learned state that is not seen in the control state. Connectivity also varies with learning, with measureable changes in cross-correlational strength between cells. After a learning experience, there can also be a washout of effects where the strength of the correlation decreased. Even though there is still much to discover about the functional formation of learning phenomena, many critical questions have been addressed. The questions that are important to rehabilitation include the following: Does learning involve hierarchical ordered stages and processing operations or dynamic systems? Are there neuronal assemblies or

pathways that represent movements and thoughts and are they dynamic? They employ large populations, but how are those populations interconnected and how do they play against each other or with each other? In the few sections that follow, we attempt to describe the current state of knowledge in this field, focusing on the matters most relevant to rehabilitation.

Learning that is relevant to recovery

Motor learning involves the development of new sequences of movement elements. Whether the elements are defined kinematically, or in terms of motion, force, or muscle activations, or are a combination of these things has not yet been clearly elucidated. One question is what kind of motor learning is needed and what factors influence relearning rehabilitation after stroke?

For example, ongoing research is demonstrating that age impacts the degree of recovery after stroke. There is evidence in the literature that training-dependent plasticity is decreased in the healthy elderly population.¹⁸ However, healthy adults at any age show a capacity to adapt, and this capacity appears to be preserved in stroke survivors.^{19,20}

One idea may be to transform the brain into a chemically “younger” brain for a better functional recovery after brain injury, perhaps via drugs. Nervous stimulation before training has been modulated in an attempt to enhance cortical excitability. In a series of experiments, 2 hours of sensory stimulation increased the degree of plasticity.²¹ The most extensively studied sensory-stimulating drug by far is dextro-amphetamine.²² In chronic stroke patients after 30 minutes of training, there was an increase not only in training-dependent plasticity but also in acceleration in the development of training-dependent plasticity when dextro-amphetamine was administered. Other drugs, such as neuopenaparine and adamoxaphine, are being tested and show preliminary promise in the laboratory setting.^{23,24} They support a role for norepinephrine in enhancing cortical plasticity and suggest potential benefits in using these drugs for improving motor recovery after stroke.

Robotic therapy strategies based on motor learning principles

Robotic therapy strategies are ad hoc and improvised for a particular situation. Motor learning is not, however. It has underlying principles that might, if they were well understood, lead to the development of rigorous strategies that optimize training. Reduction of error, for example, could be applied to tasks that are unsafe to try without some sort of assistance. Learning also might be accelerated. Robotic devices such as the MIT-MANUS and Lokomat now include second-generation controllers that try to adapt the level of assistance more intelligently to the ability of the patient based on a measurement of error. The devices nevertheless are still ad hoc methods that achieve only modest gains. With robotic therapy, Fugl-Meyer upper extremity scores increase only 2 or 3 points following robotic intervention within 300 days after stroke, after which improvement levels off.

Robotic therapy training gains may be enhanced by basing training algorithms on models of learning that define a simplified motor task, mathematically identify mechanisms of motor adaptation, and derive robotic interventions that enhance adaptation.

A simplified motor task asks a person who is holding a lightweight robotic arm to reach while the robot applies a force field that produces partial tier velocity in a direction that is perpendicular to the tier velocity. The effect is to create a curved reaching path. In articles published in 2000 and 2001, both Thoroughman and Scheidt showed that the evolution of trajectory error could be modeled with a difference equation.^{25,26} Similar error dynamics can be demonstrated for stepping in a force field that pushes up the foot.²⁷

These error dynamics minimize a cost function that balances accuracy and effort. The force that is exerted on the next movement is equal to the previous force that has been adjusted by an error factor. So if a patient steps too high, he will try to reduce the force. If he steps too low, he will try to increase the amount of force. The neural computation that minimizes this cost function includes “error-based learning” and “forgetting” terms.

Data indicate that, depending on the strength of the force field, the final error in adaptation depends linearly on the strength of the force field, reflecting that the nervous system is not only concerned about error adaptation but is also concerned about the effort expended. It seeks a sort of top level of optimization.

Techniques to improve learning may be focused on reducing errors, such as large kinematic errors, that inhibit motor training by making it too dangerous or discouraging. An example is gait and balance training that cannot be practiced if a subject cannot stand and walk safely. A learning optimization approach would derive a controller that assisted as needed using a cost function, allowing the subject to learn the force field without experiencing large errors. It is therefore possible for a healthy subject to form an internal model while experiencing small errors,²⁸ as long as a robot controller assists as needed based on sensed error and as long as it “out forgets” the human controller so the human does not let the robot do all the work. The problem of “assisting as needed” may be expressed as an optimization problem.

Accelerating learning

Because learning is error-based, increasing error may accelerate learning.²⁵ This type of recovery may be analogous to learning an internal model at a computational level if a new set of neural activations moves the limb as desired. However, the time constant of rehabilitation is much slower: 1000 seconds of reaches over days instead of 10 seconds of reaches over minutes. The difference in dynamics is likely due to a strengthening-like process. Actuator saturation limits the ability to implement an internal model, so neural strength is what is fundamentally required. If strengthening is the key process that limits recovery after a stroke, then the objective of training is not necessarily to enlarge muscles but to get more signal to the muscles.

Applying mathematical techniques to rehabilitation

The goals of rehabilitation training are to maximize the number of repetitions as well as the patient’s attention and effort. These variables compete, however, when a robot provides assistance. For example, if a Lokomat is providing rigid assistance, a patient relaxes and stops paying attention.

The goal is to design robotic devices that minimize patient error in order to maintain a reasonable number of repetitions and practice and to minimize robotic force so patients continue to exert effort and pay attention to what they are doing. Computational models are needed to understand fatigue, slacking, and error-based learning; more agile robots also are necessary to shift from rigid to more compliant assistance.

Error amplification techniques

Studies over the last 5 years have demonstrated that much of motor skill acquisition is task selective and task specific. In addition, the intention to move is important for improving motor function. Much less is known about the patients who will benefit most from constraint-induced therapy and the ultimate time window for improvement. It is unclear how much training or intensity is needed for each or different types of patients or how much the size of lesions may affect functional outcome.

Constraint-induced therapy may be seen as a form of error amplification, because humans are bimanual and bipedal and therefore have inherent redundancies. Task error is small even if only one hand is available, and forced use of an impaired limb makes task error large.

It is difficult to understand how amplifying errors in the performance of tasks that are nonredundant will improve recovery. However, a study showed that stroke-impaired reaching paths could become straighter using error amplification.¹⁹ Stroke patients were guided by a robot to reach out to a target while forces amplified the curvature of the movement. In this study, patients adapted to the force field to a greater extent when errors were amplified than when errors were decreased. Patients in this study were not asked to reach the target by as straight a path as possible, so an unconstrained part of the task was altered. Error amplification therefore may bring the attention of a subject to some aspect of a task that is being neglected and that is insidious to long-term health and performance.

Nevertheless, not all patients with stroke are able to make use of explicit and implicit information in the same way. Some patients with subcortical lesions, for example, cannot use explicit information at all. So broad learning rules may not apply to certain patients depending on where the lesion is located and whether cognitive deficits are related to motor and sensory deficits.

Moreover, analytical approaches that describe the process of learning adaptation in the short term may not be realistically applicable to the infinitesimally small changes that take place with recovery over the long term.

A paradigm for providing assistance-as-needed rehabilitation for doing rigorous and verifiably optimal training with a robot may serve as a foundation for defining essential relationships, such as the relationship between error or success and learning, and for more directly choosing therapy algorithms.

Although such a paradigm is too finite for application to humans, it has potential as a system for conducting research on patients who have gradations of impairment in motor control, whether it is for the upper extremity or the lower extremity. This approach would allow researchers to look across the ability to compensate for errors based on a measure of actual motor control or strength or speed of movement and help identify the minimum amount of motor control that one needs to be able to benefit from a training paradigm.

Structural Changes in Muscle and Adaptation

A skeletal muscle resembles a crystal with arrays of myofilaments that allow researchers to measure structural changes and infer functional alterations. Such measurements are critical in rehabilitation research and medicine because so much of therapy relies on tendon transfer as muscles are moved in an effort to restore function. A muscle has an optimal length for force generation; if it is over- or understretched during a transfer or manipulation, the amount of force generated by that muscle can be dramatically compromised.

Skeletal muscle force changes associated with length are highly nonlinear. If a muscle is shortening, there is no way to tell if muscle force will increase or decrease; muscles can get shorter and stronger or shorter and weaker depending on the sarcomere length range over which they operate. Sarcomere length and operating range are basic principles underlying neural/motor control. They are fundamental features that the neuromuscular system maintains by means of the adaptive capacity of skeletal muscle.

Laser diffraction as a probe for structural changes

To explore some of the questions associated with muscle adaptation during manipulation, a tool consisting of a low-power laser beam and a photodetector system has been placed inside a muscle during surgery on the upper extremity. The device illuminates and images in real time a diffraction pattern that serves as a manifestation of sarcomere length. If bundles of muscle fibers are destroyed, there is no diffraction pattern because the crystal structure of muscle has been destroyed. Laser diffraction therefore has a built-in quality control. A bundle of muscle fibers produces a strong diffraction pattern when the sarcomeres have been kept in regular spacing. A device that measures the spacing between diffracted orders determines the length of the sarcomeres within the skeletal muscle.²⁹

Intraoperative measurements of skeletal muscle have been taken in normal human volunteers and in humans undergoing tendon transfer. In patients with tennis elbow, who are treated as normal patients because their muscle appears to be fairly normal, sarcomere length as a function of the angle of the wrist joint when the wrist is nearly fully flexed has been compared to the angle when the wrist is fully extended. When the wrist is extended, sarcomere length decreases. When the wrist is flexed, the length of the sarcomere is the same as it is when it generates almost no force. The sarcomere actually generates maximum force when the wrist is near full extension.

The notion that muscles generate their maximum force in the mid-range of joint motion is an assumption that has support only in scientific studies of the muscles used by swimming fish, which vibrate at optimal length, and in literature concerning heart muscle, which operates at a relatively short sarcomere length. In limb muscles, however, there are few data to indicate this relationship.

Adaptation in chronic spasticity

Dramatic changes occur in skeletal muscle secondary to chronic spasticity due to stroke, head injury, cerebral palsy, and spinal cord injury. However, the structural basis for the changes in the cellular mechanics of muscles has not been elucidated. Completely neglected in the muscle world is an appreciation of the interaction between muscle and the extracellular matrix. Clearly, there is communication between the two. Muscle cells transmit their forces via the extracellular matrix to the tendons and to the outside world, and any rehabilitation strategy comes from the outside world through the bones, the tendons, and the extracellular matrix to the muscle fibers. The nature of the communication in the muscle fiber/extracellular matrix interface is very important yet very poorly understood.

Much of the data on the adaptation of spastic human muscle to chronic cerebral palsy have been collected in studies of children. Anecdotal data from a variety of stroke and head injury patients show that the most severely affected stroke patients exhibit changes in muscle that are similar to those seen in children with cerebral palsy but head injury patients do not.

Although spasticity is neural in origin, one may consider muscles themselves to be smart tissues as they continually adapt to the stress, strain, and loading history that are imposed upon them and as they try to adapt their structural properties to accomplish functional goals. To determine what is going on at the tissue level inside muscles that are highly shortened, experiments compared intraoperative flexor carpi ulnaris (FCU) measurements in children who had wrist flexion contracture and those who had normal wrist flexors, such as those who had lost wrist extensors because of radial nerve injuries but who still had normal flexors. In these experiments, "normal" FCU muscles were 2.4 μm in length but spastic muscles were 3.6 μm when the wrist was flexed.

Some of the literature on muscle spasticity has concluded that muscles adapt to maintain optimal length. When a muscle changes its structure and ultimately obtains a highly unfavorable sarcomere length (i.e., it has a highly shortened muscle and highly stretched sarcomeres), motor function is dramatically altered. Motor function is altered simply because of a chronic change in sarcomere length. This observation has profound implications for the function of the wrist joint.

The possibility that the fibers within spastic muscle have been so stretched out that they change their intrinsic mechanical properties was tested using methods developed by Brandt in the 1970s, which assess biopsies of human skeletal muscle. Forty-one biopsies were taken from normal volunteers and 12 from patients with spasticity. Single-cell segments were dissected in a high adenosine triphosphate (ATP) intracellular “relaxing” solution. Cells then were elongated in 250- μm increments, and the slope of the stress–strain curve was measured. In this study, the resting length of the sarcomere was shorter in biopsies from patients with spasticity, and the sarcomeres bore almost twice as much stress as normal muscle cells. Muscle fibers therefore became shorter and stiffer secondary to a central nervous system lesion. The extent of the change in sarcomere length was sufficient to alter function. Spastic cells also were smaller in general than normal cells, so stress was normalized at the cross-sectional area.³⁰ Nevertheless, spastic muscle cells did not bear higher loads than normal muscle cells, even though the spastic cells were dramatically stiffer. This reflects a general issue in muscle physiology: the lack of understanding of the rules by which whole muscles are built from muscle fibers.

In a study that compared the mechanical properties of single muscle fibers versus small bundles of muscle cells as well as the surrounding extracellular matrix, spastic cells were twice as stiff as normal cells, but normal bundles were much stiffer than the spastic bundles. This implies that the overall mechanical properties of muscle tissue are not simply the sum of the properties of individual muscle cells.³¹

Specimens of normal muscle tissue are composed primarily of muscle fibers (95% muscle and 5% extracellular matrix), but specimens of spastic cells have more extracellular matrix (60% extracellular matrix and 40% muscle cells). Although normal fibers bear about half the stress of a spastic fiber, they have so little normal extracellular matrix that the extracellular matrix ends up bearing stresses in the 8 GPa range. The extracellular matrix is of such inferior quality in spastic cells, it bears much lower stresses (0.2 GPa).

How can researchers determine the extent to which muscle and extracellular matrix contribute to the mechanical properties of skeletal muscle in normal volunteers and spastic patients? One way is to use collagen-degrading enzymes to eliminate collagen before mechanical loading. In both normal and spastic cells, a significant fraction of load-bearing capacity is lost after the basement membrane has been lost. However, there is still a difference in the tangent modulus between normal and spastic cells. Spastic cells have a tangent modulus of 40 kPa, and normal cells have a tangent modulus of 20 kPa after the administration of collagenase. The conclusion is that something other than the extracellular matrix is bearing a significant load.

The principle load-bearing protein in skeletal muscle is titin, which varies in different types of tissue. For example, titin in heart muscle is very stiff, whereas the titin in limb muscles is more compliant. Initial studies that measured the molecular mass of titin in normal muscles and the mass in spastic muscles found that normal titin was longer than spastic titin, and there was a weak correlation between the size of the titin molecule and the mechanical properties of the tissue.

Intraoperative sarcomere length measurements provide insights into joint function and can assist during tendon transfers. Muscles from patients with spasticity have a large number of

abnormalities, both in vivo and in vitro. Sarcomere lengths in vivo are abnormally long, which at first glance would point to some abnormality or disruption of the normal sarcomere length-regulating apparatus. Sarcomere length is highly regulated. Whether sarcomere numbers are also highly regulated is not known. However, sarcomere numbers are extremely important in terms of joint function, and they are altered as a result of chronic neural change. The decreased resting sarcomere length and the increased tangent modulus in vitro suggest a role for cytoskeletal proteins, including perhaps titin. The extracellular matrix from the spastic muscle occupies a large fraction of area. The extracellular matrix in spastic cells is hypertrophic, but its mechanical properties are inferior to those of normal cells by a factor of >40.

Muscle response to increased loading

Muscles respond to increased loading from an adequate stimulus, such as resistance training or an occupational activity, by getting larger. Muscles also change their phenotype from relatively fast to relatively slow motor units. In the normal course of events, skeletal muscles will adapt to what they are seeing as far as loading is concerned. They will increase if they are loaded more; they will decrease if they are loaded less. The shift from slow to fast occurs when an individual with less muscle still needs to be able to generate a fair amount of power. Fast muscle fibers, although they are not economical in their use of energy, can produce more power relative to slow myofibers.

Studies have examined the effect on proteins, such as myocin, during changes in muscle loading state to track function. In general, an increase in the amount of this protein is associated with increases in the force capabilities of muscle. A shift in phenotype to myosin heavy chain protein determines whether a myofiber will be fast or slow. The way muscles adapt, whether to an increase or decrease in loading, is through the amount and character of the proteins that are expressed. Muscles that are getting larger degrade their fast myocin heavy chains and replace them with slow heavy chains. Muscles that are getting smaller have a decrease in overall muscle protein production.

There are three principal pathways that regulate muscle adaptation. One of these has to do with self-repair signaling. In other words, muscles that sense changes in their activity actually change the signaling pathways around themselves. One of the ways muscles do that is by producing insulin-like growth factor 1 (IGF1) in the local environment to signal its host cell as well as neighboring and satellite cells.

Downstream from this type of signaling is the phosphorylation cascade, which increases the translation of mRNA and increases the ability to mRNA to enter into ribosomes and trigger the development of proteins. Other signaling pathways can impinge upon mRNA translation or change transcription to turn on an anabolic process. Cells also receive communication through hormones and growth factors.

A potential avenue for this communication involves interactions between the extracellular matrix and integrins in the cell membrane that are attached to signaling pathways within muscle. In this way, deformation of the extracellular matrix may be transmitted to the nuclei in the muscle fibers to indicate that there has been a change in the loading state. This process would activate a new transcription program leading to the production of proteins that are appropriate for an appropriate response. Such a generalized system would allow the communication of actual loading mechanical changes to the nuclei so that the muscles sense their environment.

Other components of the IGF1 system include binding proteins that increase the half-life of the IGF1, so that it will not be flushed out of the muscle and can continue to interact with the receptors. p76 is a critical signaling protein that will lead to an increase in the production of

components of the ribosomes, which in turn increases the capability to make more proteins. When p76 is phosphorylated, it is highly activated, so it can be used as marker of anabolic tendencies in the skeletal muscle.

The 4e binding protein is inhibitory. When 4e binding protein is hypophosphorylated, it prevents mRNA from getting into ribosomes and fueling the production of protein. When it is hyperphosphorylated, it is removed from mRNA, so mRNA can get into the ribosome, be translated, and made into protein. These two proteins are, therefore, key markers of anabolic responses that are highly sensitive to increases in loading. This is an area of active research as data increasingly are indicating that cytoskeletal elements within muscle are integral to signaling. Even in the case of IGF1 signaling, some of the components of the process are localized on parts of the cytoskeleton that are linked to the cell and are sensitive to deformation. Key factors for muscle response to increased loading are localized growth factor expression in skeletal muscle and the ability to make more protein, which can be limited by the amount of RNA or ribosomal RNA that is available. The regulation of translation seems to be exquisitely tightly held in muscle fibers.

Longitudinal growth of muscle

The rehabilitation world is very myopic in that it tends to concentrate on the radial growth of muscle or the loss of the radial dimension in muscle atrophy rather than to explore the longitudinal growth of skeletal muscle. In contrast with literally thousands of basic science studies on radial growth, probably fewer than 100 papers have explored longitudinal growth in skeletal muscle. Radial growth adds myofibrils in parallel, but longitudinal growth adds sarcomeres in series. A major research challenge is to learn how muscle understands when it should add sarcomeres or myofibrils in parallel.

Longitudinal growth of skeletal muscle may be responsible for the contractures that occur during distraction osteogenesis. Distraction osteogenesis uses a series of rings that are connected with one another through a set of rods with bone pins that penetrate the tibia. After creating a fracture in the bone, the distraction rod forces the rings away from one another to increase the so-called distraction gap and actually causes bone to grow. In some cases, however, the foot drops into the equinus position; so while distraction osteogenesis corrects a limb length deformity, it may also cause the equinus contraction, which requires many hours of rehabilitation or surgery to correct. Longitudinal growth of skeletal muscle may be a factor if, during the distraction process, the tibia is being lengthened at a rate that is faster than the rate at which muscle can add sarcomeres in series or grow longitudinally.

In one animal experiment, distraction was conducted at two different rates: 0.25 mm per day and 0.5 mm per day. In the first group, there was an increase in muscle length of 21 mm and an increase in fiber length of 12 mm. In the second group, muscle length increased 31 mm and fiber length increased 22 mm. The two groups nevertheless ended up with the same final sarcomere length of 2.7 μm , suggesting that there is a set point at which sarcomeres begin to grow.

A series of experiments looked at the changes in the architectural properties of muscle after 4, 8, 16, and 32 days of distraction. After 4 days, when sarcomere length was 2.8 μm , all animals had the same number of sarcomeres. After 8 days, animals in the slow distraction and control groups had the same number of sarcomeres, but the animals in the fast distraction group had a significant increase in the number of sarcomeres, which happened to coincide with the plateau 2.7 μm sarcomere length. Sarcomere number began to diverge for the animals in the slow distraction group when sarcomere length reached 2.65 μm . These data suggest that once a certain amount of strain is exerted on the muscle or the sarcomere, the muscle will begin to add sarcomeres in series with one another.

A question that remains unresolved at this point is whether the addition of sarcomeres occurs throughout the myofibril or only at the ends of the myofibril. Does it occur at specific junctions or randomly?

Satellite cell hypothesis

A typical fiber in a brachial radialis muscle is about 100 μm and has 10,000 to 20,000 myonuclei per millimeter. A huge avenue of untapped research involves the signals that are responsible for adding or losing myonuclei. While muscle fibers have the ability to add or lose myonuclei through satellite cells, there is no understanding of why a cell would do that. Experiments have looked at cell cycle regulation. Satellite cells become activated, replicate their DNA, and produce daughter cells that then fuse and become part of the myonuclear milieu of the muscle fiber. The control of this process is a wide open area of interest.

The satellite cell concept, which postulates that increased mechanical activity somehow stimulates the satellite cells to produce daughter myonuclei to fuse with the adult cell and cause the addition of sarcomeres in parallel, describes a radial growth phenomenon. It is not known whether the same concept applies during longitudinal growth or indeed if satellite cells are a prerequisite for longitudinal growth.

One way to try to understand the activation and control of satellite cells is to take a look at cell cycle genes using tissue microarrays, which have the ability to screen for the activation of upwards of about 30,000 genes. A powerful microarray technique examines a network of genes, sometimes referred to as pathways or maps, and shows some of the key genes that are responsible for the transition from a G1 to S phase of cell replication. Critical genes for the initiation of the cell cycle are cyclin D and CDK 46, while P 21 and GAD 45 inhibit the cell cycle.

If satellite cells must be stimulated to replicate themselves before muscle growth can occur, then cyclin D should be turned on and P 21 and GAD 45 should be turned off when a muscle fiber is being stretched. However, after 8 days of distraction, P 21 and GAD 45 are turned on. If the satellite cells are being inhibited by the action of these genes, then it is possible that the longitudinal growth of the muscle fiber itself is being inhibited.

In addition to their role in regeneration and cell proliferation, satellite cells also are important for skeletal muscle adaptation to increased loading. When loading increases, the satellite cells are stimulated to express muscle-specific proteins and to fuse with muscle fiber to produce muscle fiber that has more contractile proteins so it can generate more force.

In animal experiments, the soleus muscle responds to increased loading by hypertrophy to a remarkable extent, much more than the hypertrophy that occurs following general resistance-type training protocols. There is a significant increase in the expression of the RNA signal for IGF1 isoform that is specific to muscle and highly sensitive to changes in loading. This process signals the muscle to make more protein and the satellite cells to proliferate. It also signals satellite cells when to stop proliferating and begin differentiating and fusing with myofibers. Satellite cell proliferation and fusion seem to be an obligatory process for muscle hypertrophy.

Still, much about the fundamental ways in which muscles function, normally as well as under diseased conditions, has not been determined. The ultra-structure of muscle has been defined as a series of myofibrils, each having a cross-sectional area of about one square micron and rows of repeating contractile structures known as sarcomeres that extend from one Z line to the other. However, an area that has not been resolved in the muscle biology world is the pattern of sarcomere genesis. What muscles do for a living is generate force and respond to mechanical signals. It is still unclear, however, how muscle acts and reacts.

The time course of observed changes helps to determine the mechanisms by which muscles adapt to injury and disease. Although physiologists have done an excellent job in recent years to describe the molecular properties of muscle contraction (e.g., by means of studies of motor molecules), the properties of some whole muscles are still fairly poorly understood. As we gain an understanding of these processes, it will help answer several core questions regarding rehabilitation of stroke survivors: How can rehabilitation be designed to train muscle that has been altered secondary to a change in the properties of those muscles as a result of a stroke model of disuse or decreased use? How plastic is muscle if, in a diseased state, it is unloaded by being wheelchair-bound for 15 or 20 years? Is there a limit to the adaptive changes within the muscle, whether they involve myosin, fiber type, muscle size, or satellite cell proliferation? Could these factors be reconstituted by appropriate types of loading stimulation, or is there a point at which adaptation is no longer possible? In plegic patients as well as in patients who have fatigue without movement, how much of that fatigue is central, how much is related to an upper motor neuron problem with fewer descending pathways and decreased excitability of motor neurons, and how much is related to muscle fiber type that may increase fatigability?

Biomechanics

Beyond muscle at the fiber level, an enormous problem in stroke rehabilitation is the lack of understanding of the biomechanics of movement of the lower as well as the upper extremities. In terms of locomotion, clinicians and researchers are hampered by the inability to define and quantitatively assess the major impairments that exist following stroke. Walking needs to be defined in terms of the integral subtasks that reflect the performance of underlying neurological systems, as well as the subsystems that are functionally important to the task and that can be differentially impaired, so the identification of the functions that have been specifically affected can be more quantitative and specific. Then clinicians can decide whether rehabilitation is correcting the underlying problem and determine whether a rehabilitation device is addressing the mechanical and functional issues that are most important for a particular patient.

One approach is to develop quantitative assessments that would effectively discriminate between varying abilities and demonstrate a correlation with the clinical judgment of important tasks, such as balance control or the generation of appropriate stepping, so changes in locomotion could be assessed reliably across groups of patients and treatment sessions for individual patients and reflect the mechanics underlying the walking task. For instance, measurement of the generation of propulsion while walking could be based on such forces as anterior/posterior ground reaction. Ideally, by breaking up the subtasks of locomotion into systems according to the underlying nerve physiological substrate, the individual needs of the patient might be targeted more specifically, the effects of rehabilitation might be monitored more directly, and the design of rehabilitation devices might be more efficient.

With a level of an understanding that allows targeting of not only the walking task or a complex multifactorial output like walking speed but also the specific deficits a patient has, the integration among controllers for position versus impedance, pattern constraints and modes of setting, and passive motion of the legs might be much more logical. Breaking down the locomotion task into biomechanical subtasks also might help identify the specific activities a robot could perform and provide measures in the robotic environment that would differentiate between the functions that are improving and the ones that are not.

Neuroimaging

It would be helpful for clinicians planning therapy to be able to predict what will happen with a patient after a stroke and to gauge, based on the patient's status at the time of injury, what might be the best therapy and then to determine at the outset of therapy how far he or she may progress in the future. Among the positive early clinical predictors of recovery are voluntary

movement within 2 weeks, especially in the upper limb, return of wrist and finger extension within the first month, isolated as opposed to synergistic arm and finger movements, and a Fugl-Meyer score greater than 19 at 1 month. Among the negative predictors of recovery is the inability to grip the hand after 1 month. It is interesting to note that lack of leg movement at 1 week is a negative prognostic sign for the return of upper limb function, and a Fugl-Meyer score of less than 10 is a negative prognostic sign.

Behavioral endpoints are the most meaningful for stroke patients, but clinicians and researchers need to dig beneath the topsoil and get to the roots of what is being done during rehabilitation if they are to learn how to do it better. An understanding of the relationship between therapeutic intervention and injury is also needed to maximize behavioral gains. Systems-level data from functional neuroimaging, brain mapping, and even anatomical studies that connect behavior and molecular events offer ways of getting that extra level of insight.

Neuroimaging and transcranial magnetic stimulation (TMS) provide some indication of the potential for recovery after stroke. Small infarctions in the distribution of the middle cerebral artery (MCA) are associated with better outcomes than larger infarcts. For infarctions that occur outside the distribution of the MCA, size does not appear to be as clear a predictor of outcome. The location of a cerebral lesion on neuroimaging studies has been linked with outcomes, with recovery far more likely among patients who have lesions in the cortex than in the corona radiata or the internal capsule, even though some patients with lesions in the internal capsule do well clinically and patients who have small cortical strokes may be hampered by other problems such as cognitive, communication, visual or perceptual deficits, and/or apraxia. The presence of a lesion in the basal ganglia predicts a better outcome than one in the internal capsule; however, this distinction is not a clear predictive factor. Although motor-evoked potentials on TMS are not used clinically on a regular basis, they have been predictive of improved recovery when they are present in higher amplitudes and shorter latencies.

But does neuroimaging or TMS offer information that cannot otherwise be gleaned from clinical assessment? Indeed, a neuroimaging sign may be highly predictive and indicate that a patient would benefit from a particular therapeutic intervention. But if the same decision can be made on the basis of a clinical sign that is just as good a predictor of patient response, then why would a clinician waste money and time by employing a neuroimaging technique?

Data from neuroimaging investigations, including brain mapping following physiological stimulation of the cortex, anatomical MRI or computed tomography (CT) mapping, functional assessments of brain activation with MRI, positron emission tomography (PET), or single photon emission CT (SPECT), examine the connections between injury and subsequent central nervous system (CNS) responses as well as the structure and function of the CNS.

Functional imaging obtains systems-level data that may help in triaging therapy, comprehending the biological factors that influence the effects of therapies and interventions, and determining the scope, intensity, and scheduling of therapeutic interventions. At the systems level, functional imaging reveals patterns of brain activity that may be important to the task of rewiring or repairing damaged cortical connections. In one study, fMRI demonstrated the differences in activation of a motor circuit after injury to the CNS. The study compared brain activation in 11 patients who were classified as American Spinal Injury Association Level A after a spinal cord injury and 12 healthy control subjects when they tried to move their right foot. More pronounced changes occurred in the left sensorimotor cortex among control subjects, but activity was similar in the thalamus in both groups.

Neuroimaging findings may relate eventual treatment outcomes to the extent of injury to a particular system. In one study, Crafton compared fMRI and anatomical descriptions of injury volume and demonstrated that functional mapping was more strongly correlated with

behavioral outcome than the total volume of the infarct.³² Although the volume of an infarct was considered to be moderate in one patient at 33 cc, the infarction involved 35% of the proportion of the motor map that was involved in hand movement. Early changes in TMS after two 90-minute sessions per week predicted final clinical gains in a study by Koski.³³ The normalization of motor-evoked potential asymmetry following therapy was associated with long-term improvement in Fugl-Meyer scores in this study.

Neuroimaging, especially fMRI, may provide insight into the mechanisms of stroke as well as the mechanisms and effects of motor relearning after stroke to help understand the physiology of recovery, as it reflects changes in pre- and posttherapy motor imagery. Functional imaging has the potential for revealing whether a specific cognitive or physical task engages, excites, or inhibits activation patterns in regions of interest within normal systems and maps reorganization in relation to the intensity and duration of the treatment. In relation to dose response with robotics, functional imaging may answer questions such as: Did we do enough therapy? Did we do too much therapy? Did we perform a therapeutic intervention that actually engaged the network we are interested in? It is also likely that functional imaging will offer a look at pharmacologic and physiological patterns of treatment effects, and it may be a surrogate for examining the processes of plasticity and a potential predictor of capacity for plasticity.

However, although fMRI, TMS, and other forms of surrogate assessments indicate what may be driving neurological networks over time, it is not clear whether they can be used on a routine basis to predict the outcomes of therapy, because there is no probe test that is relevant to the skills that are targeted for training. Too often the outcome measure for showing improvement in motor function is the Barthel Index (see ref. ³⁴), which does not require the patient to use the affected body part to carry out a task, so it has nothing to do with the individual task. Statistically significant morphing of a singular physiological event, TMS or PET or MEG finding, or some statistical representation therefore cannot presently serve as a surrogate measure for clinically important behavioral gains.

What's Ahead

What are some of the most important questions for trying to decide whether robotics will be clinically accepted in stroke rehabilitation? A major question is how researchers can develop robotic interventions that produce not just statistically significant but clinically effective improvements in targeted functions. Clearly, gains should be more robust when using a robotic device than when using another intervention, and they should be compared with control interventions that are relevant to the ways in which patients can be trained.

Clinical and functional relevance

The best recovery from a physiotherapist's or clinician's point of view involves practice that is not only repetitive but is also functionally relevant in order to engage the nervous system. The nervous system does not focus on the degree of contraction of the biceps or triceps when reaching forward; it thinks about getting a task done. The more the patient is motivated to perform a task, the more the nervous system is engaged. If the goal of robotic therapy is to diminish impairment, then repetitive practice using robotics can be effective.

Perhaps there should be two classes of robots: robots that diminish impairment, and robots that improve function. Increasing the strength of key muscles in the lower extremity has been correlated with functional improvement with respect to walking, speed walking, endurance, and so on. However, the same gains and strengths in the upper extremity have not been related to improvements in function. Except for improving key patterns of movement, the strength of muscles does not necessarily have to be increased in the upper limb but the coordination and dexterity of the muscles do. So it is not the maximal voluntary contraction that is important,

but instead it is the appropriately timed production of adequate agonist/antagonist activity throughout a movement that is most relevant for a task. For these reasons, robotic therapy can be combined with task-oriented therapy.

Neural control, viscoelastic properties, and hypertonia

Functional motor tasks, even simple ones such as reaching, may involve multiple neural control mechanisms in the regulation of different aspects of motor behavior. There is some preliminary evidence that posture regulation deficits after a stroke can have serious negative impact on the generation of smooth goal-directed trajectories. These postural constraints on trajectory formation and final position acquisition pose unique challenges for the restoration of functional movement. In one study, all four neurologically intact patients exhibited greater variability in the preferred limb than in the nonpreferred limb. However, 11 of 12 stroke survivors had greater variability in the nonpreferred limb. The difference in variability in the final positioning depended on whether proprioception was intact or impaired. Coefficients of the model also depended on whether the patient had an MCA stroke versus a lesion that impacted basal ganglia and the hemisphere in which the lesion was located. A careful study of how impaired activation and coactivation of antagonist muscles in the arm impact the trajectory formation in final position regulation has yet to be undertaken.

Studies have shown that stiffness and viscosity are modulated independently. A robot was programmed to slowly position the hand of a relaxed arm in a number of different locations in the reachable work space for 5 seconds. The EMG activity and the hand force were then recorded for a neurologically impacted subject and for a representative stroke subject. In the healthy individual, the relaxed limb generated only nominal force; in the representative stroke subject, postural forces were high and they had a complex spatial topography. Shoulder and elbow joints and elbow muscles were active over much of the work, exhibiting up to 44% of maximum voluntary contraction in one case.

These position-dependent forces likely reflect abnormal reflex threshold phenomena. So, for example, if a patient wanted to move the hand into a specific region of the work space, not only would the triceps have to oppose the forces generated by the flexors in that location but it would also have to generate enough force to accelerate the limb into that position of the work space.

This line of reasoning has important implications for the execution of simple tasks such as the generation of goal-directed movements. To perform a desired movement, the best way to move the free hand of this viscoelastic actuator depends on the stiffness and damping viscosity coefficients. Under normal conditions, when the joint angular damping is at its nominal value, the limb would reach its desired position after tweaking the set point in a relatively short amount of time. When the joint viscosity increases as a result of elevated co-contraction, movement slows down dramatically, especially as the hand draws near its goal. This effect could be reduced, in part, by increasing the drive at the beginning of the movement. It is uncertain whether this would be a desirable strategy, because it might exacerbate the subsequent agonist/antagonist co-activity. A better option would be to train patients to produce individuated agonist and antagonist co-contractions throughout the reachable work space.

Can explicit knowledge of the topography of the hypertonic response and position-specific individuation training facilitate functional motor recovery following stroke? Here the role of the robot would be to move and hold the hand in a disadvantaged position so the patient could train on isolating activities of the agonist and antagonists. The efficacy of this training would be determined by examining how well patients could generate movements into or against or along with the gradient of hypertonia.

Brain imaging tools

The state of the art for quantifying changes in brain images to make predictions is fMRI, which identifies increases or decreases in regional activity qualified by volume or intensity of signal. Scalar and distributed geometrics are being explored as methods of providing multivariate physiologic measures.

A scalar measure, or a laterality index, is a way to characterize brain function by left or right hemisphere activity. An index of activity may be produced by adding together all the activity in the SMA, dorsal, ventral, and pre-motor cortices, CMA, and so on, and comparing a scalar measure of motor cortical activity as a function of total activity. Scalar measures are useful in clinical trials to derive quick and straightforward clinical values. The brain may be viewed as Euclidean space to generate a normative map and plot points within a 10-dimensional space to reflect changes in activation pattern over time.

Linking imaging and robotics

In one scenario, well-defined imaging of the brain structure that has been affected by a stroke may identify an area of neglect and a certain type of behavioral deficit. A robot may then provide a training approach that is consistent with that behavior. In another scenario, perhaps a more futuristic one, an adaptive machine may be used to identify the aspects of behaviors that have been affected by a particular lesion and provide information about them.

Models of relearning

Within the area of relearning technology, there are techniques such as constraint-induced therapy and body weight-supported treadmill training, virtual reality, and robotics. In addition, there are biologic facilitation techniques such as brain stimulation, pharmacology, and cellular therapy. As scientists and clinicians pursue research in these areas, it would be helpful to know the kind of physiological impact that is being exerted on processes within the CNS. Physiological investigations within clinical trials in stroke rehabilitation and neuroimaging would be valuable; however, it is difficult to justify the use of expensive tests in addition to a clinical trial. Animal research therefore will be essential for conducting investigations that place the interpretation of physiological findings in the context of rehabilitation interventions. The more these types of investigations can be linked together, the better, because ultimately the goal is to have clinical trials inform clinical care.

New areas

One of the issues to address in research is the development of a model that might allow the premotor cortex to function like the primary motor cortex. A computerized model of stroke may be augmented by providing the brain-computer interface control with visual and proprioceptive feedback.

Sensory experience may also provide a pathway for recovery. Researchers have shown that the way sensory input is processed after a stroke or a spinal cord injury is very different than the way it is processed in a nonimpaired system. Are there rules that govern the way these new nervous systems process sensory input? Are the processes significantly or only slightly different in the unimpaired and in the diseased state? Patients after a stroke or spinal cord injury are much more dependent on sensory input. For example, they are not able to walk with the trunk bent over. Without an upright, stable trunk, there is no recovery of walking or a stepping pattern.

Nevertheless, an understanding of motor systems such as central pattern generators and their interaction with sensory information will identify strategies for early recovery, perhaps when brain input is not able to re-teach the motor task to drive plasticity. Researchers are

rediscovering that intense weight-bearing rehabilitation makes a difference, even among patients with incomplete spinal cord injury. The challenge for investigators is to understand what strategy is best at each stage of recovery for a patient population.

Another key challenge for robotic development is the need for continual change. Repetition in and of itself is not sufficient for recovery. There must be adjustments to changes in function, and the nervous system must adapt to its environment independently. Such cross-training is not well-suited for this early stage of scientific testing, where conditions need to be well controlled. It is likely that combined therapy elements will have to become part of any good rehabilitation program.

Because some therapists are more skilled than others and get better results, we can speculate that improvements may have little to do with rehabilitation tools and more to do with the appropriate cues from the therapist. If the recovery process is more cognitively based, an inviting new idea is to involve the therapist in the robotic experience, creating a trio of participants. Experiments that concentrate on important sensory cues are attempting to measure what a physical therapist does and incorporate it in teaching a robot to change over time.³⁵ Other experiments seek to develop interactive approaches that may take advantage of the intelligence of the therapist. A phase-specific excitation of afferents, which capitalizes on the fact that patients are more sensitive to those types of inputs, tries to retrain extensors during extensions and flexors during flexion. EMG data are similar for therapists and a robotic device, suggesting that robotic devices may be fashioned to produce patterns similar to those utilized by therapists that result in appropriate locomotion.

As engineers create robotic devices that are more sophisticated, researchers need to ask themselves what they really know about progressive training of a skill using a robot versus some other rehabilitation technique. Perhaps more sophisticated robotic devices are not needed, but we need evidence that shows a difference in one strategy compared to another.

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