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Motor rehabilitation after stroke, traumatic brain, and spinal cord injury: common denominators within recent clinical trials

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Abstract

Purpose of review—Experimental studies and clinical trials that aim to improve motor function for use of the upper extremity and walking are traditionally separated by the category of neurological disease. This boundary may deter investigators from finding common denominators in the conceptual basis and deployment of rehabilitation interventions, especially across nonprogressive diseases in adults, such as stroke, brain trauma, and spinal cord injury.

Recent findings—The results of recent randomized clinical trials for walking by treadmill training and robotic devices and for the upper extremity by constraint-induced therapy, robotics, and brain stimulation suggest that more efficient strategies are needed to devise and prove the value of new therapies.

Summary—Investigators should consider working across disease platforms to develop and test the most optimal methods for training patients, the most practical trial designs, the best dose–response characteristics of interventions, the most meaningful outcome measures, and the likelihood of transfer of trained performance to real-world settings. Clinicians in the community may be more likely to adopt evidence-based practices drawn from positive trial results if these treatment strategies focus on key motor impairments and related disabilities, rather than on diseases.

Keywords

functional electrical stimulation; gait training; robotics; spinal cord injury; stroke rehabilitation

Introduction

Focal brain injury from stroke, diffuse and focal disconnections from traumatic brain injury (TBI), and the multilevel, localized intramedullary lesions of traumatic spinal cord injury (SCI) tend to be considered within the confines of each etiology of disease over the course of neurological rehabilitation. Although pathoanatomic and physiologic differences unfold within the initial days and perhaps month after onset in animal models, these diseases share similarities in the cascades of injury-related and regeneration-associated gene expression, immune responses, recovery of cellular and synaptic function in partially injured regions,

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the effects of milieu inhibitors and enablers of plasticity, mechanisms for protecting, strengthening, and creating neural connections, and the effects of training and experience on learning motor skills [1–4,5•,6,7].

Adult, monophasic neurological diseases such as stroke, TBI, and SCI each affect different populations by age and sex and have different distributions of postinjury medical, social, impairment, and functional problems, but these differences are mostly bumps in the rehabilitation process to return patients back to a higher level of self-care, mobility, and participation. Although the common loci of lesions obviously differ across these diseases, the extent of injury to the motor system and to motor-related cognitive networks often overlaps. For voluntary and fine motor control, it matters little where the corticospinal tracts are interrupted compared with the amount of damage. In addition, SCI *per se* does not affect cortical networks for cognition, but one-third of patients with a SCI have an associated TBI. Although the cognitive impairments after stroke may be less diffuse than after TBI, considerable repetition that uses multiple sensory modalities is often needed by both groups to try to build declarative and procedural memory. In both diseases, memory deficits are partially a result of interrupted inputs and outputs from the hippocampus [8].

Most important, the mechanisms of motor and cognitive control and the neural adaptations that accompany training and learning are not dependent on a disease as much as they rely on spared nodes within neural networks. Indeed, the usual practice paradigms employed during rehabilitation therapy to try to enable better reaching, grasping, walking, and more complex patterns of movement tend not to differ. Therapeutic concepts such as task-oriented training, progressive practice to increase movement speed and precision, compensatory adaptations, strengthening, and cardiovascular fitness are engrained in the rehabilitation goals for patients with most neurological diseases [9,10]. The design of clinical trials and strategies for the rehabilitation of sensorimotor impairments and related disabilities, then, may be able to take a more interactive and collaborative approach regardless of the underlying neurological disease. Indeed, greater insights from basic and clinical studies might be unlocked by opening the fences that divide, by disease, how we harness findings relevant to neuroplasticity that follows and can be induced after stroke, TBI, and SCI [11]. This review emphasizes what might be appropriated from the results of some recent randomized controlled trials (RCTs) that may be especially relevant to neurorehabilitation for motor gains. These potential lessons apply in many ways to motor studies of amyotrophic lateral sclerosis [12], multiple sclerosis (MS) [13], Parkinson's [14], and other progressive neurological diseases.

Common denominators in motor learning

A primary strategy for the rehabilitation of sensorimotor impairments and related disabilities is to put patients in a position to be able to practice and continuously improve upon their motor control and skills [15]. The neural substrates for gains exist within the context of spared neural pathways and compensatory adaptations [16•]. Regardless of the disease, rehabilitation takes advantage of a fundamental feature of neural circuits, which is the capacity for adaptations within and across neurons and their synapses in response to experience, training, and learning. The sensorimotor networks engaged in improving

performance and consolidating skills are highly integrated with other systems that represent aspects of cognition, including working memory, executive functions such as planning and task-switching, error and novelty detection, reward and motivation, responsiveness to verbal and physical cues, and language. Research aimed at motor gains must consider how to work around differences across patients in regard to the extent of injury within these interconnected circuits, then develop therapeutic methods to optimize the incorporation of recovered and remote pathways into a training paradigm that leads to a well powered RCT [17–21]. Indeed, regardless of the disease and location of injury within the sensorimotor network, the degradation of signal processing and the need for altered strategies to perform a task may lead to the recruitment of neural networks, as revealed by functional neuroimaging studies [22–28], although the relationship between recruitment and behavioral changes is still moot.

Confounders of gains may be shared by diseases of the motor system as well. For example, competition for learning resources during skills retraining, and perhaps saturation for learning at a molecular level, may reduce effective gains when training several related skills simultaneously [29]. The same confounding effect may occur when one specific type of training competes with daily activity that employs a different, suboptimal strategy for practice in reaching or walking. In animal models of stroke and SCI, training in these different contexts has led to poorer outcomes than expected [30] or may produce motor habits that compete or substitute for successful movements [31]. Fatigue is another potential confounder that may interfere with practice and learning in patients with stroke, SCI, TBI, and MS. One type of fatigue includes the perception of tiredness and lack of endurance that may be intertwined with motivation and mood disorders. Limitations on practice also arise with fatigability that takes the form of muscle weakness from repetitive use of the upper or lower extremities [32].

Thus, rehabilitation paradigms to treat motor impairments and related disabilities across diseases are anticipated to overlap in their strategies to enhance similar skills and to reduce confounders of training-induced gains.

Common denominators in recent clinical trials

The best evidence to date is that any form of physiotherapy at a high enough dose is more likely to reduce impairment and disability than no rehabilitation intervention [33]. Specific approaches to improve in particular motor-related tasks and outcome measures, however, are the proper focus of programs of rehabilitation after stroke, TBI, and SCI. Recent trials of forms of exercise and of task-oriented training that have been or could be applied to these and other neurological diseases are reviewed.

Exercise

Therapeutic exercise can aim to increase fitness, strength, balance, and mobility, and enable patients to relearn how to perform a skill or task.

Aerobic conditioning

After stroke, TBI, and SCI, conditioning effects have been achieved in subacute and chronic patients by exercises that include treadmill walking, stationary cycling, and arm ergometry [34–37]. Aerobic conditioning has been achieved by exercising only the upper extremities after SCI, but most readily by adding functional electrical stimulation to enable pedaling against resistance after paraplegia. The point of fitness is to build some reserve and tolerance for exertion during daily activities, in addition to the benefits of disease prevention, such as enabling the control of blood pressure, glucose utilization, and the metabolic syndrome.

The results of RCTs across neurological diseases and aging also suggest that aerobic activity can improve aspects of cognition [38], diminish the decline of aspects of cognition and learning associated with aging [39], and lessen depression. Thus, a routine aerobic exercise may not only improve motor function and daily activities, but also lessen the rate or degree of subsequent decline as patients age with their residual disabilities. The underlying cortical mechanisms for motor and cognitive improvements, drawn from rodent experiments, include increases in dopamine, noradrenergic, cholinergic, and serotonergic neurotransmitter activity, the expression of trophic factors such as brain-derived neurotrophic factor (BDNF), activation of receptors that regulate genes to modulate memory such as calcium/calmodulin-dependent protein kinase II and phosphatidylinositol-3-kinase, and the promotion of neurogenesis, angiogenesis, and synaptogenesis in the hippocampus and perhaps other regions [5•,40]. The subsequent behavioral changes in models of disease and aging vary in type and degree, but include motor speed and learning, cognitive processing speed, and auditory and visual attention. RCTs in patients with neurological diseases, however, have yet to go beyond intriguing pilot data. This suite of potential exercise-related actions may enhance procedural and declarative learning when combined with task-oriented rehabilitation interventions, as well as help maintain skills and fitness as patients with stroke, TBI, and SCI age with their chronic impairments and disabilities. Of great interest, drugs that activate several identified pathways for gene regulation of the effects of exercise are becoming available for clinical testing [40].

Strengthening

The principles for muscle strengthening do not differ across patients with neurological diseases or from what healthy persons must do. Both the affected and unaffected limbs can benefit from strengthening exercises. A so-called unaffected arm or leg may be weakened by disuse as well as by mild loss of descending motor control. The approaches to training will depend on the ability to move against gravity or to offer at least some resistance for eccentric or concentric muscle contractions. Rather simple exercises include lifting more than 50% of the maximum load a person is capable of for a single movement for 8–12 repetitions in two to three sets as progress allows. Task-specific practice for walking may be augmented by strengthening key muscle groups such as the hip and knee flexors and extensors. Despite many small trials, however, the optimal strategies for deploying strengthening exercises to improve functional activities remain moot [41,42]. For example, is selective muscle strengthening by using weights or elastic bands preferable to adding resistance during the practice of functional movements? The answers will apply regardless of the underlying disease.

Task practice

Repetitive task training has been found to be beneficial primarily in studies of stroke, but through 2006, the effect sizes derived from controlled trials have been modest for walking and upper extremity outcomes [43]. Confounders of these studies include low power to detect differences between treatment arms, the adequacy of intensity and duration of the experimental intervention, and the general finding of lesser differences when an active control intervention is utilized compared to no specific practice paradigm [9]. Most RCTs enter patients who are mildly to moderately impaired, rather than at the lower end of the scale of motor control, where the need for clever interventions is greatest. Improved planning of pilot studies for task-related training may lead to RCTs that have a better chance to reveal robust differences between the new experimental intervention and an active, alternative intervention [44•]. Such pilot studies can test therapies in parallel and sequentially across diseases to build upon each investigator's learning curve.

Use of the upper extremity

The Extremity Constraint Induced Therapy Evaluation (EXCITE) trial showed that 10 full day sessions over 2 weeks with 60 or more hours of upper extremity practice that increasingly shaped more complex movements in the hemiparetic arm, plus about 6 h per day of forced use at home by gloving the unaffected hand, led to better function of the arm and hand compared to no therapy in patients who were 3–9 months after stroke [45]. Subsequent reports showed that the improvements were retained and that patients who were entered even a year after onset also improved, although without the same margin of gain. Less-intensive therapy, often called modified CIT, has been the subject of many small trials, most of which show efficacy in some measure of functional use of the upper extremity. For example, 2 h of EXCITE-type therapy daily for 15 sessions over 3 weeks, plus restraint, improved performance of the upper extremity more than conventional therapy that employed less specific, repetitive practice of the same duration and also provided restraint [46,47]. Use of CIT starting within the first 2 weeks after stroke during inpatient rehabilitation did not prove to be superior when the control dose equaled the experimental one [48]. CIT has been applied to patients with TBI, SCI, cerebral palsy, and MS in pilot studies [49]. By merging the insights of all trials, perhaps a most optimal approach to shaping, practice, constraint, dose of treatment, control intervention, and outcome measures can be found.

Robotic assistive devices have been developed in many forms to try to maximize the amount of practice for reaching movements [50,51]. Commercially available devices have yet to show greater efficacy, however, than an equal amount of more conventional practice when the outcomes are related to functional use of the arm and hand, as opposed to small gains in strength [52,53•,54]. A RCT of a three-piece training device in patients after stroke with low Fugl-Meyer motor scores will be reported in early 2010 [21]. Strategies for the carryover of practice when using these devices to arm and hand practice and daily activities without the device have not yet been established. This transition seems critical to any proof of concept or efficacy trial. More cooperation among engineers who develop these devices with clinicians who can establish training protocols and test for generalization of effects will be needed, regardless of the cause of the upper motor neuron etiology of paresis. Also,

inexpensive and cosmetically acceptable robotic exoskeletons or commercially available functional electrical stimulation (FES) devices for wrist extension and hand grasp are reasonable approaches for patients with marked loss of motor control, especially when combined with task-related training [55–57]. Here again, the level of motor control and disability, not the disease, is what matters.

Focal cortical excitation and inhibition by transcranial magnetic or direct current stimulation have shown some promise in small trials to increase learning of specific movements. The protocols for stimulation and the combination of practice in relation to the timing of the stimulation have varied widely [58,59]. A well designed RCT of direct stimulation over the primary motor cortex of the hand using implanted dural electrodes failed to improve outcomes when used to augment simultaneous rehabilitation [20,60]. This setback suggests that protocols have yet to find the optimal stimulation parameters and type of patient. Indeed, regardless of disease, what investigators must establish are the minimal amount of intact motor-related neuronal pools, corticospinal axons, and residual voluntary movement needed for stimulation strategies to improve functional movements. The incorporation of these techniques to augment motor or cognitive gains could move faster into definitive efficacy studies if larger problem-solving pilot studies across diseases that affect movement were funded to engage more experts [61•].

Motor imagery [62], bimanual practice, and virtual reality systems for practice have also been employed primarily in upper extremity pilot studies to engage reach and grasp activities. Imagery aims to recruit the same network that would be activated if the task were performed voluntarily, but for patients with brain lesions, these techniques may be especially difficult, depending on such issues as attention, residual networks, and circadian rhythms [63]. Most pilot studies of these interventions have been carried out in a small number of patients after mild-to-moderate stroke, using simple tasks. Thus, proof-of-principle studies have limitations to date. The procedures for training and learning, once established, however, may not differ across diseases if the capacity of the patient to perform is present.

Walking

Treadmill training with partial body weight support (BWSTT) has been studied across neurological diseases in large and small trials, including stroke [19,64], SCI [65,66], TBI, cerebral palsy [49], and MS. The results to date for trials in which the control group receives an equal opportunity to practice walking reveal little difference in end points such as walking independence and speed, however. The Locomotor Experience Applied Post Stroke (LEAPS) trial [19] for patients with stroke who walk at less than 0.8 m/s at entry 2 months after the onset will be reported in late 2010 and should, finally, point to whether or not this training strategy, combined with over-ground practice, can increase the level of functional walking compared to more general exercise. Of interest, this trial's investigators looked carefully at the design and training strategies of prior RCTs of BWSTT for stroke and SCI, incorporated valued aspects, and reworked potential flaws.

Treadmill training has led to the use of electromechanical robotic devices to try to maximize the number of steps practiced with more normal kinematics than the patient might be

capable of during full weight bearing over ground. Many such devices are being tested, but initial well designed trials that compared the Lokomat and the Gait Trainer have not revealed greater benefit on walking outcomes compared with equal intensity of over-ground training after stroke [67,68•,69,70], SCI [71], and MS [72,73]. Small trials have also tested a virtual reality addendum to robotic and treadmill training, reporting modest gains in the experimental VR group.

Pilot studies in SCI, stroke, MS, TBI, and cerebral palsy often use unspecified strategies to reinforce best stepping parameters when training patients on a treadmill or robotic device. It is also uncertain what therapists intend to transfer from training on the device to practice over ground and *vice versa*. This process ought to be an iterative one that mutually builds improvements in the pattern, safety, speed, and endurance for walking. The relative failure of robotic assistive devices to markedly improve mobility to date may rest in the difficulty of enabling greater learning compared to practice without them, because movements are highly repetitious and restrained by the characteristics of the device. Learning may be more difficult to internalize and to generalize to other movements when practice is rather inflexible, even if the number of repetitive movements is greater than without robotic-assisted training.

Controlled trials are especially needed to test these novel additions to conventional training compared with only conventional over-ground training in patients with minimal motor control more than 3 months after onset. The impairment cohort that most needs better interventions to accomplish walking is the one that can only produce minimal to partial movement against gravity at the hip and knee flexors and extensors.

Cross-breeding may produce better trials and care

Clinical rehabilitation trials that are built upon concepts of neuroplasticity to improve motor control and related outcomes share many complex requirements, regardless of the neurological disease. Techniques drawn from any particular research model may be less dependent on the type of disease or proposed scientific basis for the intervention than on the residual motor control of the patient and the ability of the therapist to enable progressive shaping of movements for a range of skills with practice. These issues can perhaps be best addressed by more interaction among investigators who develop and test the many variations of rehabilitation strategies [11]. Pilot studies could provide a more productive path toward robust clinical interventions, as well as end futile pursuits sooner, if investigators iteratively built upon the details of each other’s most promising approaches as experiments proceeded. For example, if the dose of one therapy produced a clinically modest gain, the next pilot study might double that dose in a similar cohort or in a cohort that appeared likely to benefit based on prior studies. The subsequent effect size of that therapy for one disease at a defined level of impairment and with similar outcome measures may then better predict the likelihood of effectiveness for another disease. Also, new outcome measures or statistical designs drawn from pilot studies can be assessed and applied to other diseases that aim to improve similar targets. For example, the use of dichotomous outcomes is being tested based on stratification of initial walking speed in the LEAPS trial [19]. More controversially, but with fair justification, the recent frampidine RCT for MS

planned a responder versus nonresponder analysis for walking outcomes [74]. If such designs prove successful, they can serve other studies.

A concern in rehabilitation is that evidence-based practices are not readily adopted by community therapists [61•]. This issue is apparent throughout medicine, especially for complex interventions. For example, dispensing tissue plasminogen activator to be given within 3 h of stroke onset caught on slowly in the community over 10 years, despite very positive efficacy trials. Many of the newer strategies for rehabilitation of motor control are just as complex and expensive, if not as potentially dangerous. Thus, therapists and physicians have to grow comfortable and skilled in providing specific new exercise or task-oriented therapies, along with robotic, external stimulation, computer-based, and other rehabilitation approaches. Clinicians may be more likely to adopt new valued techniques if the same intervention can be applied across a spectrum of pathologies.

Conclusion

The pipeline for translating research models drawn from the basic sciences into valid pilot studies, then smart RCTs, and finally into standard clinical practice requires more bidirectional inputs at every level [61•,75]. Genuine collaborations among experts from the laboratory tributaries that feed the pipeline seem an obvious strategy for progress, with less regard to the barriers that have evolved based on disease categories. Funding agencies could promote this interaction by opening opportunities for investigators to develop collaborative approaches to solve rate-limiting problems, in addition to funding single laboratory-initiated discovery research [11]. Clinical scientists could then develop and test interventions for impaired motor function within and across diseases to better assess the confounders and opportunities for developing robust therapies. Greater acceptance of new interventions by therapists and rehabilitation payers may follow once well defined, common-denominator therapeutic strategies can be titrated to fit the needs and capabilities of any patient.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 685).

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