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Training and exercise to drive poststroke recovery

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SUMMARY

To make practical recommendations regarding therapeutic strategies for the rehabilitation of patients with hemiparetic stroke, it is important to have a general understanding of the fundamental mechanisms underlying the neuroplasticity that is induced by skills training and by exercise programs designed to increase muscle strength and cardiovascular fitness. Recent clinical trials have provided insights into methods that promote adaptations within the nervous system that correlate with improved walking and upper extremity function, and that can be instigated at any time after stroke onset. Data obtained to date indicate that patients who have mild to moderate levels of impairment and disability can benefit from interventions that depend on repetitive task-oriented practice at the intensity and duration necessary to reach a plateau in a reacquired skill. Studies are underway to lessen the consequences of more-severe motor deficits by drawing on medications that augment plasticity, biological interventions that promote neural repair, and strategies that employ electrical stimulation and robotics.

Keywords

exercise; functional MRI; motor control; muscle strength; stroke rehabilitation

INTRODUCTION

Disability associated with hemiplegia or hemiparesis markedly limits independent living and social participation in at least half of all stroke survivors.¹ In turn, reduced levels of exercise and daily activity as a consequence of disability can increase risk factors for recurrent stroke, cardiovascular disease and diabetes mellitus. Arm and leg weakness and imbalance can be accompanied by pain, joint contractures, disuse atrophy of muscles, spasticity with dystonic limb postures, falls and fear of falling, and other complications. At least some of these complications might, however, be avoidable.

Within several days after the onset of a stroke, clinicians can begin to promote functional recovery in their patients. It should be possible to tap into fundamental cellular and molecular events associated with injury in an attempt to lessen impairments,² such as the weakness and loss of coordination resulting from hemiparesis, and disabilities, such as

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limitations in the use of the affected upper extremity for self care, or slow and unsafe ambulation. Recent randomized clinical trials have provided insights into methods to improve mobility, cognitive and motor skills, strength and fitness.¹ Many effective and low-cost strategies can be put in place in the months following a disabling stroke, which can help patients to advance along a course towards greater functional recovery. In most hemiparetic patients, the trajectory of improvement can begin within a few days following the stroke, and can continue during structured inpatient and outpatient rehabilitation aided by therapists. Over the subsequent months and years, by identifying the skills they need (e.g. faster and safer walking ability for longer distances) and setting specific new functional goals (e.g. engaging the affected hand in more tasks), patients can increase and optimally maintain their ability to participate in home and community activities.

This Review provides a framework to help clinicians and their patients consider and exploit some of the basic neurobiological mechanisms that could enhance the course of motor recovery and independence in daily activities. The interventions described in this article aim to optimize adaptations within the cerebral, spinal and peripheral neural systems to enable skilled movements, within affected muscles to increase strength and endurance, and at the systemic level to improve cardiovascular fitness. The scientific rationales behind, and the practical procedures for, specific training approaches are likely to be perceived differently by different clinicians. Some interventions might be more applicable to patients with particular sensorimotor and cognitive impairments, but elements of task-specific practice, and strengthening and fitness training can be applied to most patients at any stage of poststroke rehabilitation.

BASIC MECHANISMS OF NEUROPLASTICITY

Initial motor gains after stroke might result from the resolution of reversible injuries to neurons and glia, such as alterations in membrane potentials, axon conduction or neurotransmission. Reorganization of spared assemblies of neurons that represent motor actions within the sensorimotor cortex, as well as in transcortical, ascending and descending pathways, seems to accompany further improvements in motor skills.³ Contributions from more widely distributed cortical and subcortical regions, including cerebral systems for perception, attention, motivation, executive planning, working memory, and explicit and implicit learning, might be required to compensate for strategies that the injured brain can no longer support. The ability to strengthen muscles and reach an appropriate level of cardiovascular fitness also depends on these nonmotor systems. A brief overview of several of the mechanisms that enable neuroplasticity might help us to focus on creative ways to enhance recovery of function in patients with hemiparesis.

Adaptability of the building blocks for movement

The skeletomotor system in humans includes at least seven separate descending corticospinal tract pathways. The descending cortical systems seem to rely heavily on intrinsic pattern generators and motor primitives organized within the motor pools of the spinal cord.⁴ These spinal systems provide automatic movements across joints, such as rhythmic, alternating flexion and extension of the limbs for stepping.⁵ Cortical motor neurons within the sulcus of the primary motor cortex (M1) orchestrate flexible pattern

generation by modulating the more-automated actions of the spinal cord.⁶ Lesions of the corticospinal pathways cause loss of movement patterns, along with weakness, fatigability when performing repetitive movements, and loss of multijoint coordination, especially of the elbow, wrist and fingers for reaching and grasping, and of the knee, ankle and toes for walking quickly at low energy cost.

Corticomotor pyramidal neurons in layers 3 and 5 of M1 for any single muscle are broadly distributed over many millimeters. Collections of neurons that innervate the spinal motor neurons of a single muscle intermingle with those that innervate other muscles across one or more joints.⁷ This organization allows neurons that innervate different muscles to learn new and finer movement patterns together, bound by Hebbian long-term potentiation, and other mechanisms that determine synaptic efficacy. The redundancy created by overlapping supraspinal descending projections can be used to relearn a movement pattern when some of M1 or the corticospinal pathway has been infarcted.⁸ Indeed, if enough of their pathways have been spared, other parts of the distributed cortical and subcortical sensorimotor system can be recruited to drive the motor pools in the spinal cord. In addition, uncrossed fibers of the corticospinal tract (right cerebral M1 fibers that descend in the right ventral white matter of the cord and tend to innervate axial muscle groups) and axons that recross (right M1 fibers that descend in the left corticospinal tract, enter the ventral horn, and cross under the central canal to homologous motor pools on the right) might provide input that can partially compensate for the loss of motor pathway function.⁹ For example, functional imaging studies of children with cerebral palsy and after hemispherectomy (Figure 1) suggest that the uncrossed or recrossing pathways can subsume considerable function.¹⁰ These bilateral effects might explain the findings of a meta-analysis of 16 well-controlled studies, which showed that 15–48 sessions of strengthening exercises in one arm or leg in normal subjects also strengthened the opposite limb to about half the extent of the trained side.¹¹ Interhemispheric connections via the corpus callosum between most cortical motor areas might also contribute to this gain.

If an adequate residual percentage of ascending sensory and descending motor contributions are present (at least 15% of axons in the dorsal and lateral spinal columns, say), carefully chosen practice paradigms might enable adequate reaching and grasping with the hand, and walking. In general, training must aim to optimize the control of spared ascending feedback and descending neural controllers.

Functional brain mapping

Functional neuroimaging studies have revealed robust examples of regional cortical plasticity associated with sensorimotor gains and training protocols. Investigational findings vary according to the location and severity of anatomical loss, the activation task used during a functional MRI study, and the intensity and duration of a specific rehabilitation intervention.^{12–14} Studies in patients soon after the onset of hemiplegia, for example, often reveal progressive changes in activation of the supplementary motor area, dorsal premotor cortex, cerebellum, thalamus, and—if they have experienced a cortical stroke—on the peri-infarct rim of M1. Impairment in behavioral performance correlates positively with the degree of shift of activation contralesionally to homologous M1 neurons and primary

sensory cortex (S1). Improving motor skill is associated with an increase in ipsilesional activation of the primary sensorimotor cortex (M1/S1) that probably reflects an initial representational expansion, followed by greater focusing of activity in this region if skilled movements recover.¹⁵ Figure 1 shows adaptations over a period of locomotor training in M1/S1 in a youngster with hemiparesis who had undergone a hemispherectomy for epilepsy 4 years earlier. The left hemisphere controlled the ankle movements of both lower extremities (Figure 1A). With training on a treadmill and over ground for 2 weeks, the representations for ankle movement of each lower extremity enlarged and came to share similar territories in M1/S1 (Figure 1B), consistent with animal studies of activity-dependent plasticity.^{7,8}

The best outcomes are achieved in patients with the most sparing of the corticospinal tract.¹⁶ Indeed, clinically, if no wrist or finger extension—which are dependent on the corticospinal path—has evolved by 4 weeks after a stroke, it becomes highly unlikely that hand function will be regained. Transcranial magnetic stimulation can be employed to determine the amount of intact M1 and to test for changes in its excitability during retraining of motor skills.¹⁷

Biological changes

In animal models of stroke, M1 and related motor cortices and the spinal cord evolve robust changes in their structure and function in response to specific types of motor training.¹⁸ Skills training induces synaptogenesis, synaptic potentiation, and reorganization of movement representations within the motor cortex.⁷ This plasticity supports the production and refinement of skilled movement sequences. Strength training, by contrast, can alter the excitability of spinal motor neurons and induce synaptogenesis within the spinal cord, but does not alter the organization of the motor map. Initial strengthening might depend on improved descending control of a movement before a change in muscle mass occurs.¹⁹ Strength training can increase both the rate of torque development and the discharge rate of motor units. The ability to vary discharge rate markedly influences the fluctuations in force necessary for the submaximal contractions that are required to perform everyday tasks. The main effect of resistance training is to increase the volume of muscle fibers in response to stress-related gene expression.²⁰ Endurance training improves cardiovascular parameters of fitness, but does not alter the organization of the motor representation or number of synapses. Fitness training might induce changes in spinal reflexes, depending on the particular behavioral demands of the task. Different types of practice and experience, therefore, differentially affect the distributed sensorimotor systems, and this experience-specific plasticity offers opportunities to enhance recovery after stroke.

Experimental studies indicate that the biological changes associated with practice-induced plasticity are molecular (e.g. changes in gene transcription, protein regulation or neurotransmitter release), morphological (e.g. growth of dendritic spines associated with long-term potentiation at synapses), and physiological (e.g. excitation and inhibition among assemblies of neurons). Exercise, at least in relatively inactive caged rodents, leads to changes in gene expression, including upregulation or downregulation of genes encoding molecules associated with learning and memory, and also to neurogenesis.^{2,21} These

changes occur both in healthy animals and in animals that have undergone induced focal cerebral infarction. For example, brain-derived neurotrophic factor is upregulated by exercise. This growth factor modulates the function of intracellular signaling systems such as calcium-calmodulin kinase II and mitogen-activated protein kinase, leading to the activation of cAMP response element-binding protein, which functions in a critical pathway for learning, synaptogenesis and axonal sprouting. Exercise and skills learning mediate multiple integrated responses in neural systems, as well as cardiovascular, endocrine, immune and other physiological systems, all of which might promote cerebral reorganization, synaptic efficacy, and recovery of function after stroke.

The biological responses to exercise in patients might be less pronounced than those in relatively experience-deprived, genetically homogeneous laboratory animals. Responses are also likely to depend on how long after stroke the exercise is initiated, the amount of exercise therapy administered, and the duration, type and context of the task that is practiced by a patient.²² Clinicians should emphasize to patients that practice has powerful influences on the biology of the nervous system, and that these adaptations can be induced to varying degrees at any time after stroke.

TASK-ORIENTED PRACTICE TO IMPROVE SKILLS

In terms of improving daily functioning, task-specific training seems to benefit stroke patients more than does general exercise, as it does in healthy subjects who wish to learn a new motor skill. One of the problems in demonstrating the specific effects of practice of any given task across rehabilitation trials has been the low intensity of training, which might limit the robustness of outcomes.²³ The minimal duration of a task-related rehabilitation therapy for a subacute impairment or disability should generally exceed 18 h of practice, but much work needs to be done to determine the optimum dose–response effects of specific interventions. In addition, responsiveness to training has been observed mostly in patients who have retained reasonable motor control, such as being able to at least partially extend the wrist and fingers or flex the hip and extend the knee on the hemiparetic side.

Upper extremity function

The Extremity Constraint Induced Therapy Evaluation (EXCITE) trial systematically tested a task-oriented neurorehabilitation therapy among patients who were able to initiate extension movements at the wrist and fingers.^{24,25} Subjects had sustained a first stroke 3–9 months before enrollment. The experimental constraint-induced therapy (CIT) intervention involved a mitt that prevented use of the unaffected hand for 90% of waking hours for 2 weeks. In addition, this intervention employed 6 h a day of highly structured, therapist-led, progressive and repetitive adaptive practice. Training involved gradual approximation of subcomponents of upper extremity task-related movements, subsequently progressing to the practice of fuller movements as these became feasible. Practice tasks included 40 well-defined activities. In addition, the CIT group was instructed to practice specific upper extremity tasks after each daily session and to aim to solve problems that limited the use of the affected hand throughout the day at home. On completion of the intervention, the CIT group was given a home program of tasks to practice for 30 min daily using the affected hand. The intensity of training for a compliant subject could reach 60–80 h of upper

extremity practice in the 2 weeks of CIT, another 6 h a day of forced use at home for 14 days, and 15 h a month of functional activities using the affected hand for 11 months, before the primary outcome measures were obtained. The control group in EXCITE received no formal training or instruction, partly owing to fiscal constraints.²⁶

Statistically significant and clinically relevant improvements in paretic arm motor ability and daily use were observed in individuals receiving CIT; lesser improvements were observed in participants receiving usual and customary care. In addition, the improvements following the 2-week CIT intervention persisted for at least 1 year and were not influenced by age, gender, or initial level of paretic arm function.

In summary, a well-constructed, intense, and task-oriented skills learning intervention that was shown in smaller studies to be associated with cortical reorganization, as measured by functional MRI and transcranial magnetic stimulation, proved to have at least moderate clinical benefits compared with almost no specified practice.²⁷ CIT can take other forms in terms of intensity and the nature of the task-related practice, but trials of these variations have been too small to enable the most important components of the strategy to be determined.²⁸ In addition, task-oriented practice has been provided by a range of robotic assistive devices that can improve proximal arm strength and reaching.²⁹ More-sophisticated devices are currently in clinical trials.

Walking

Task-oriented training for walking after stroke has included activities to improve balance and stepping. Practice in walking along courses with modest obstacles might improve balance and walking speed in outpatients who want to improve their sense of safety. Gait practice with rhythmic auditory cues, similar to marching music, can also improve walking variables.³⁰ For patients with more-severe disabilities, step training on a treadmill belt with partial bodyweight support provided by an overhead harness allows considerable stepping practice. The paretic leg can be unloaded to prevent buckling. A therapist can help position the foot and assist knee control throughout the step cycle. The subject can concentrate on repetitive practice of hip flexion for leg swing, knee flexion and extension, heel strike at the end of the swing, and other gait components (see Box 1). Studies to date show modest improvements in walking speed in chronically disabled, slow walkers after six or more weeks of training on a treadmill, but the results have not been superior to those of the same intensity of over-ground practice alone in patients who were randomized on admission to inpatient rehabilitation after stroke.³¹ A large randomized American trial known as LEAPS (Locomotor Experience Applied Post Stroke) is in progress to optimally compare treadmill training involving partial weight suspension plus over-ground gait training, with nonwalking exercises, in hemiparetic subjects 2–6 months after stroke.³²

Box 1

Devising a poststroke training program

Decide which impairments, disabilities and daily activities are reasonable goals for training

For example:

- Lower-extremity weakness and incoordination with a hemiparetic gait
- Slow walking that is effortful and makes it impossible to cross a street before the traffic light changes
- Fatigue during walking and fear of falling, which prevent the patient from attending church or visiting friends

Practice components of impaired movements of the affected limbs to achieve task-related actions

For example:

- On a mat or standing with support as needed, practice sets of 12
- isolated 10–30° hip flexion and extension movements, followed by knee flexion and extension movements
- Try to reproduce these selective flexor and extensor movements during the stance and swing phases of walking
- Aim to take steps with equal strides of the hemiparetic and opposite lower extremity

Practice should be progressive in intensity and at levels of difficulty near maximal performance

For example:

- Have another person provide slight resistance during the isolated lower limb flexor and extensor movements. Add partial squats while standing with the back against a wall
- Try to increase walking speed over a flat 30 m path every day
- Try to increase the distance walked in 5–10 min each day

Improve strength and endurance

For example:

- Exercise the lower extremity flexor and extensor muscles across each joint using the resistance of elastic bands or weights as tolerated
- Increase the time walked by a feasible increment weekly until a planned community distance equal to at least several blocks has been achieved. Walk on uneven surfaces
- Pedal a recumbent bicycle or walk on a treadmill for up to 30 min while mildly dyspneic

Electromechanical robotic devices^{33–35} aim to provide task-specific gait training by enabling patients to emulate the kinematics used by healthy subjects, and several

commercial devices are available. Small trials conducted to date have produced promising results, but have not shown this approach to be better than more-conventional training of the same intensity. Problems with robotic training include the fact that sensory feedback to aid learning is not yet feasible, robots can step the subject's lower extremities with little effort from the patient, and no systematic carry-over from robotic-driven step training to over-ground training has been offered. Step training combined with functional electrical stimulation of the ankle dorsiflexors to aid foot clearance and knee control also shows promise by at least modestly improving walking speed.^{36,37}

MUSCLE STRENGTHENING

The aim of practice is centered on the regaining of skills, but task-oriented learning should be supplemented by exercises to build muscle strength and increase endurance. Initial resistance exercises lead to improved strength before an increase in muscle fiber diameter occurs, because the ability to efficiently perform a novel task, such as lifting hand weights, requires the acquisition of new skills, including biomechanical adjustments and timing.

The principles of strengthening approaches are similar for both able-bodied individuals and people with disabilities. Progressive resistance exercise is a method of increasing the ability of muscles to generate force. The American College of Sports Medicine recommends the following strategy for increasing muscle strength in healthy individuals: first, lift loads that allow a small number of repetitions until fatigued; second, practice 8–12 repetitions of the amount of weight that can be lifted through the available range of motion before needing a rest (often about 50% of the maximum load that can be lifted once); third, exercise two or three times a week and allow sufficient rest between exercises for recovery; fourth, increase the resistance as ability to generate force increases; and fifth, monitor for adverse events including pain and stiffness.³⁸ Elastic bands offering differing amounts of resistance can be used instead of weights to optimize movements across a range of directions in keeping with hemiparetic capabilities. Increases in spasticity, such as the development of increased upper extremity flexor tone, are unlikely to occur.³⁹

A meta-analysis including both healthy older individuals and patients after stroke found that progressive resistance exercise generally improved the ability to generate force. Using methods such as those recommended by the American College of Sports Medicine, most studies showed that resistance exercise in patients with stroke improved muscle strength on the unaffected side by 20–40% and on the paretic side by 10–75%, whereas changes in muscle strength in the control group, who did not perform resistance exercise, ranged from a 5–10% gain to a 10% decline. Maintenance of functional strength might, therefore, fail without an exercise regimen.

It might be expected that the moderate to large effects of strengthening would carry over into an improved ability to perform daily activities and participate in usual roles, but this has not been definitively demonstrated.⁴⁰ It is possible that gains in strength will only carry over into other activities if tasks are practiced under the new condition of added availability of force. After stroke, for example, about 75% of the work related to the speed of walking is performed by the bilateral hip extensors in the early stance phase of gait, along with the

ankle plantar flexors for thrust on the affected side in late stance. These muscle groups could be the focus of strengthening exercises, along with efforts to improve the timing of their activation during reciprocal lower extremity stepping. Feedback during training about the timing of loading of the stance leg compared with hip flexion of the swing leg could improve step length and the symmetry of the amount of time spent in stance or swing for each leg.⁴¹ Indeed, exercise programs for low-functioning older adults must include task-specific exercise, such as walking, augmented by strengthening of key hip and knee muscles, to prevent the onset of disability with accompanying falls and deconditioning.

AEROBIC CONDITIONING

Patients often experience marked deconditioning after stroke.³⁷ Cardiovascular stress testing reveals that by several months after the onset of hemiparesis, stroke patients are unable to exceed the metabolic activity needed to perform casual daily activities. The easiest way to obtain a conditioning effect is by first walking faster as gait improves, then by treadmill walking or bicycling on a recumbent stationary bicycle with the affected foot tied into a stirrup (Box 1). In healthy subjects, cardiovascular fitness sufficient to lower the risk of heart disease and stroke can be achieved by exercise three times a week comprising as little as a 5 min warm up with stretching and 30 min of physical activity that maintains a heart rate $>70\% \times (220 - \text{age in years})$. Similar progressive aerobic exercise in patients more than 6 months after stroke led to an increase in peak exercise oxygen consumption and, within 2 months, increased the distance walked in 6 min by 30%, compared with patients who performed low-intensity walking.⁴² In another trial of patients at around 1 year after stroke, an intervention group was given a fitness and mobility exercise program designed to improve cardiorespiratory fitness, mobility, leg muscle strength and balance in three 1-hour sessions per week for 19 weeks.⁴³ The control group received a seated upper extremity program. The intervention group showed significant improvements with respect to cardiorespiratory fitness, mobility, paretic leg muscle strength, and participation in daily life compared with the control group.

Walking speed over 15 m and walking distance for 6 min are commonly used measures of walking ability after stroke.⁴⁴ Patients with hemiparesis usually walk at a velocity that is most compatible with the energy cost of ambulation. Cardiovascular fitness, balance, and paretic leg strength are independently associated with longer walking distance and walking speed during a 6-minute walk.⁴⁵ These components of exercise should, therefore, be emphasized and measured. Clinicians could easily measure the time it takes for a patient to complete a 15-meter walk (normal speed is about 100 cm/s or about 12–15 s to cover this distance) and, hence, gain insight into mobility; such a measurement could also be used to determine gains during an exercise program.

In summary, fitness training is feasible in patients with hemiparesis who are able to ambulate without human assistance. Task-related training seems to produce immediate benefits.⁴⁶ To maintain fitness and extend the benefits to cardiovascular risk management, a program of exercise must be enjoyable, safe and accessible.

HOME EXERCISE PROGRAMS

A number of randomized clinical trials have highlighted the value of exercise programs in individuals living in the community after stroke. Some studies aimed to lessen specific impairments, whereas others tried a more global approach to skills practice, strengthening and fitness. One study showed that both a 10-week supervised exercise program and a program consisting of 1 week of supervised instruction followed by 9 weeks of unsupervised exercise led to physical benefits, such as greater 6-minute walking distance. The gains persisted for at least 1 year.⁴⁷

Another well-designed trial randomized 100 individuals, 3 months after hemiparetic stroke (mean age 70 years and independent in walking), to a structured, progressive, physiologically-based, therapist-supervised, in-home program that comprised 36 sessions of 90 min over 12 weeks, or to a program of usual care. The exercise program targeted flexibility, strength, balance, endurance and upper-extremity function.⁴⁸ Both groups showed improvements in terms of strength, balance, upper-extremity and lower-extremity motor control, upper-extremity function, and gait velocity. Gains for the intervention group exceeded those in the usual care group with regard to balance, endurance, peak aerobic capacity, mobility, and participation in usual roles. These gains were modest but clinically important. The effects had diminished 6 months after treatment ended.

Another randomized trial provided a comparison between usual treatment and an intensive exercise program for balance, strength, conditioning and skills learning, starting at admission to inpatient stroke rehabilitation.⁴⁹ The intensive exercise group received four bouts of treatment totaling about 80 h during the year. Although some functional gains were apparent at the end of inpatient care, no additional improvements following the initial gains were apparent at 3, 6 or 12 months after stroke with this very modest increase in formal training.

In summary, readily applied home exercise programs can lead to improvements in variables related to physical functioning and quality of life, but the intensity of the intervention must progressively push towards these goals. The benefits are clinically significant, if modest. Most importantly, the intervention must be continued for at least two weekly sessions of exercise or restarted every few months to maintain the accrued benefits.

FATIGABILITY

Following stroke, patients often report feeling sluggish, weary, sleepy, bothered by fatigue, and having a low level of energy.⁵⁰ Scales of fatigue at any time after hemiparetic stroke indicate that 20–40% of individuals experience these feelings. Fatigue can of course also reflect a mood disorder, side effects of medications, sleep that is limited by insomnia, sleep apnea or pain, or psychosocial problems. Patients frequently have difficulty distinguishing the effect of their neurological impairment from the effects of fatigue. Sleep apnea is common after stroke, and can cause daytime drowsiness. Nightly analgesics and primary interventions for any source of pain, antidepressant medication, and occasional use of stimulants such as caffeine or methylphenidate in modest doses can lessen a daytime sense of fatigue.

Fatigue after stroke might also be considered to be a problem of fatigability that develops with even modest exertion. An exercise-induced reduction in the ability of muscles to produce force or power, regardless of whether a task can be sustained, is a common if often overlooked cause of what a patient means by fatigue.⁵¹ Variables that might influence the mechanisms of fatigability include subject motivation, weakness that alters the pattern of muscle activation, the intensity and duration of activity, and whether exertion is continuous or intermittent with rest periods. After stroke, unusual postures of the upper extremity might place a heavy load on accessory muscles, leading to fatigue in their use. Additional factors include slowed and dispersed electrical activity from the reduced number of spared axons that can drive the spinal motor pools, as well as other components of the upper motor neuron syndrome (i.e. poor coordination of motor unit firing, hypertonicity, changes in the relative contributions to net muscle torque by synergistic muscles, alterations in muscle fiber types, and adverse changes in connective tissue and joint mobility). Muscle atrophy might worsen beyond what would be expected for the degree of weakness from hemiparesis in the presence of nonuse, medications (e.g. steroids, statins),⁵² and metabolic imbalance (e.g. electrolyte disequilibrium). It might, therefore, be difficult to distinguish central versus peripheral or neural versus muscular causes of fatigability. In addition, patients and clinicians might not appreciate the impact of fatigability, because weakening of muscle forces might begin soon after the onset of a sustained activity such as walking, but the patient nevertheless continues to perform the task.

Clinicians can demonstrate fatigability by asking a supine patient to flex the hip 30° with the leg straight and then testing flexor muscle strength, or by testing the hip extensors while the patient is in a prone position. The patient is then instructed to perform 10 straight leg raises and is immediately retested for a decline in strength. If fatigability of these proximal muscles is present, this weakening will interfere with the safety and energy cost of walking. Fatigability that interferes with daily activities can be reduced by exercise to strengthen specific functionally critical muscle groups, by cardiovascular training, by using canes, splints, braces and other aids to reduce energy demands, and by avoiding continuous use of the same muscle groups during activities.

ENHANCING RECOVERY IN PATIENTS WITH SEVERE IMPAIRMENTS

The currently available rehabilitation therapies might fail to improve the motor control and skills of a highly paretic arm and hand or lower extremity. In view of the fact that training and exercise include components of neural-based skills learning, however, it might be possible to augment the effects of practice for patients with the most severe impairments in the near future. Such strategies include medications that alter levels of dopamine, norepinephrine or neurotrophic factors, and other pharmacotherapeutic strategies to augment synaptic learning^{53,54} and muscle function. Motor imagery could also be used to engage neural networks to practice specific movements,⁵⁵ and task-oriented training in virtual environments could provide feedback to aid skills learning.⁵⁶ In addition, robotic assistive devices with sensory feedback for repetitive practice are being developed.⁵⁷ Functional electrical stimulation of muscles might enable movements not otherwise possible during the practice of tasks such as reaching to grasp an object.⁵⁸ Direct motor cortex electrical⁵⁹ or magnetic stimulation⁶⁰ combined with task-related training could augment the strength of

neuronal ensembles that represent the movement. Skills training and exercise for strengthening and fitness will also have to be incorporated into future trials of biological manipulations, such as cellular transplantation, neurogenesis, remyelination and axonal regeneration, in order to optimally enhance the synaptic strength of both residual networks and newly established pathways.²²

CONCLUSIONS

Patients with disabilities as a result of stroke can improve their ability to employ the affected and unaffected upper extremity, walk, and carry out daily activities with greater skill, using exercise and practice training that activates neural and muscular mechanisms of activity-dependent plasticity and learning.⁶¹ Exercises that aim to increase muscle strength, lessen fatigability and improve fitness are also likely to enhance daily activities and general health. No specific algorithm has yet been devised to define evidence-based practices that can be added to these strategies when patients seem to have reached a less-than-satisfactory interim plateau. Greater intensity of task-specific practice aims to improve independent performance, speed and precision of activities. Robotic assistive devices and other interventions that have been supported by small positive trials might be tried to enhance gains. The overriding goal is to enable patients to improve self-efficacy, reduce their burden on caregivers, and return to their prestroke social roles. Clinicians must take full advantage of opportunities to help their motivated patients and families in this regard.

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REVIEW CRITERIA

Meta-analyses of clinical trials and more-recent trials in the literature covering hemiplegic stroke in relation to “rehabilitation”, “exercise”, “motor learning” and “functional neuroimaging” were identified through searches of PubMed. The author also drew upon his own research studies.

KEY POINTS

- Within several days after the onset of a stroke, clinicians can begin to promote functional recovery in their patients
- An understanding of the mechanisms underlying the neuroplasticity induced by skills training might help us to devise ways to enhance gains
- Task-specific training seem to benefit stroke patients more than general exercise in terms of improving daily functioning
- Task-oriented learning should be supplemented by exercises to build muscle strength and increase endurance
- A number of randomized clinical trials have highlighted the value of exercise programs in individuals living in the community after stroke
- Patients with severe motor deficits might benefit from medications that augment plasticity, biological interventions that promote neural repair, and strategies that employ electrical stimulation and robotics

Figure 1.

Functional MRI studies performed before and after locomotor training in a 12-year-old who had undergone hemispherectomy. The left side of each panel shows the right hemispherectomy, which was performed to treat epilepsy 4 years before this study. The patient, who had left hemiparesis and impaired gait, received 2 weeks (~20 h) of therapy using BWSTT and over-ground training. The scan was performed while the subject dorsiflexed his left or right ankle 10 times over 30 s, rested for 30 s, and repeated this block design sequence a total of four times. The arrow points to the primary sensorimotor cortical sulcus. **(A)** Before training, a small region of activation representing the paretic left ankle (red) and a larger region representing the nonparetic ankle (yellow) seemed to partially overlap (orange) within the sulcus and precentral gyrus of the leg representation in M1/S1, but this was a small activation compared with healthy controls. A more-diffuse SMA activation was also seen extending into the premotor area. **(B)** When the scan was repeated a day after the subject completed training, the movements of both ankles had an enlarged and overlapping representation more within the typical M1/S1 region, consistent with the subject's improvement in motor skills for walking and ability to kick a soccer ball. Abbreviations: BWSTT, body-weight-supported treadmill training; M1/S1, primary sensorimotor cortex; SMA, supplementary motor area.