Chapter 28
Rehabilitation Strategies for Restorative Approaches After Stroke and Neurotrauma

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Abstract For acute, subacute, or chronic stroke, and neurotrauma, a range of rehabilitation strategies will be essential to optimize possible benefits of molecular, cellular, and novel pharmacological restorative approaches. The neurorehabilitation strategies must be chosen to engage the targeted networks of these novel approaches, drawing upon studies of motor and cognitive learning-related neural adaptations that accompany progressive practice. Regulatory agencies and the pharma/biotech industry will need to keep an open mind about the likely synergy that will come from interleaving repair strategies and rehabilitation interventions.

For clinical trials aimed at motor restoration, outcome measurement tools should be relevant to the anticipated targets of repair-enhanced rehabilitation. Most outcomes to date have been drawn from disease-specific and rehabilitation toolboxes. In studies that include participants who are more than a few weeks beyond acquiring profound impairments and disabilities, outcome measures will likely have to go beyond off-the-shelf tools that were not designed to detect modest clinical evidence of sensorimotor system repair. This chapter describes specific rehabilitation strategies and outcome assessments in the context of interfacing them with neurorestoration approaches.

Keywords Stroke • Spinal cord injury • Traumatic brain injury • Rehabilitation • Neuroplasticity • Motor learning • Robotics • Skills practice • Noninvasive brain stimulation • Outcomes

Other chapters in this text describe novel molecular, cellular, and pharmacological approaches that may be applied to try to improve outcomes in persons with disabling stroke and neurotrauma. Here, we will concentrate on augmenting these

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approaches by neurorehabilitation interventions, primarily for studies that aim to improve profoundly impaired motor control. Indeed, one might say that the novel approaches really should be considered as methods that aim to augment rehabilitation targeted to the sensorimotor system.

Much work and money goes into preclinical experiments to generate, for example, a reproducible and safe cell type and method of delivery, as well as establish possible mechanisms of action that are associated with chosen outcomes in a model of stroke, traumatic brain injury (TBI), or spinal cord injury (SCI). When the clinical trials are planned, however, biopharma and the U.S. Food and Drug Administration (FDA) may not want to include rehabilitation therapies. Their concern is that this combination becomes a test of two different interventions at the same time, so distinguishing adverse responses and positive outcomes related to each may be difficult. More likely, however, targeted rehabilitation, through mechanisms of activity-dependent plasticity, will maximize the potential efficacy of these novel biological approaches.

On the other hand, since neurorestoration is the goal, clinical endpoints for trials may be recommended by the FDA that primarily include off-the-shelf measurement tools that were not designed for neural repair outcomes. For acute interventions for stroke and TBI, carried out within the first 2–3 weeks after onset, conventional rehabilitation therapies and clinical measures may not need major modifications. But to promote and measure gains in studies of subacute or chronic interventions for profound and presumably minimally changing impairments, more specific strategies for rehabilitation protocols and relevant outcome measures should be considered.

This chapter emphasizes approaches that may be undertaken for more severely impaired subjects whose predicted level of future function is otherwise low. These participants in a trial might have no functional use of an upper extremity or be able to walk without human assistance.

Substrates for Rehabilitation Strategies

The neural substrates for recovery, often described as mechanisms of neuroplasticity, exist within spared neural pathways and compensatory neural and behavioral adaptations. Rehabilitation takes advantage of fundamental features of neural circuits, which include the capacity to make molecular, structural, and physiological changes within and across neurons, axons, dendrites, glia, and synapses in response to experience, training, and learning. The underpinnings of neurorehabilitation have been established in animal studies of normal mechanisms of skills learning, effects of enriched environments, behavioral experience, and postinjury training that remodels neural networks at multiple levels of the neuroaxis [1]. Indeed, training and enriched environments are increasingly included in preclinical and occasional clinical protocols for repair [2, 3]. Training, exercise, and biological processes for axonal regeneration, dendritic sprouting, and neurogenesis are inherently interactive. The success of remodeling and of strengthening neural connections in humans will,

based on animal models, also depend in part on the timing of the intervention postinjury [4, 5] as well as the reproducibility of repair responses from experimental models to patients, lesion size and location, the lesion's milieu of pro and antiregenerative molecules and physical barriers, age, premorbid skills and cognitive strengths, experience since onset of injury, medications, comorbid diseases, etc. [6, 7].

The sensorimotor networks engaged in improving performance and consolidating skills in patients are also highly integrated with other systems that represent components of cognition, including working memory, executive functions, error and novelty detection, reward and motivation, perception and imagery, responsiveness to verbal and physical cues during training, and language. Cognitive impairments are common after stroke from focal lesions, prior subcortical white matter lesions, and aging. They are especially prominent after TBI with diffuse axonal injury; many spinal cord injuries are also accompanied by TBI. This degradation in connected and remote networks may have to be addressed by rehabilitation to maximize improvements in motor skills and the ability to participate in usual personal and social activities [8]. That therapy, however, may add to the complexity of a neurorestoration clinical trial. For example, if not an exclusion criteria, aphasia, impaired working memory, impaired planning, hemi-neglect, and hemianopia may interfere with motor-related rehabilitation and the process of measuring outcomes. Some evidence-based interventions exist for certain cognitive impairments, but most are less well tested than motor skills training in chronically impaired patients [9–12]. On the other hand, spared domain-general, nonmotor networks, as well as contralesional motor regions, may be overactive as patients try with effort to accomplish a task [13–16]. Modulating these regions by physical or cognitive therapies or direct cortical stimulation may contribute to rehabilitation gains [17]. The clinical examination, along with structural and functional imaging with activation and connectivity studies, can help determine the integrity of diverse networks and their adaptations over the course of interventions.

Initial trials of cellular, molecular, and novel pharmacological approaches for stroke, TBI, and SCI seem most likely to try to improve the function of a highly paretic or plegic upper extremity (UE). That need not be the only goal of the trial, but it is one for which many rehabilitation strategies have evolved to achieve an important aspect of quality of life. Participants are likely to have a highly impaired arm and hand, probably with little or no selective movement against gravity at the wrist and fingers after supraspinal lesions. On the Fugl-Meyer Assessment Scale, they might score around 15–25/66. Other participants are likely to have no movement one level below a cervical SCI. The goals of the biological approach with rehabilitation may include functional reaching, gripping, pinching, and using the UE for tasks within one's peri-personal space to eat, groom, and assist other valued tasks.

The science of biological approaches will benefit from any demonstration of restoration, such as producing movement of the wrist and fingers against gravity at one or more joints when none had existed at baseline. The participants, however, may not benefit in their daily activities if they do not regain reach, grasp and release to hold and manipulate objects or the ability to walk. An intervention that carries risk, such as invasive procedures to implant cells, must ultimately enable useful

new function. Outcome measures, however, that can detect less than functional sensorimotor gains are critical to future advancements. Rehabilitation strategies can help promote this goal.

Neurorehabilitation Strategies

Rehabilitation is usually a multidisciplinary team effort led by a neurologist or physiatrist. That team might consider, for the individual participant in a trial, ways to quickly neutralize or reverse impairments that may interfere with the goals of the biological approach. This might include managing modest contractures, hypertonicity, muscle atrophy and disuse weakness, deconditioning, pain in joints from overuse, depression, anxiety, medications that may interfere with the actions of the biological approach or with learning and attention, and modest cognitive and perceptual impairments that interfere with daily activities.

Specific rehabilitation strategies to improve motor-related functions have common denominators after stroke, SCI, and TBI, but are primarily effective for persons with mild to moderate impairments [18]. These strategies usually include progressively more challenging task-related practice, repetition with feedback about aspects of performance using physical and verbal cues, and meaningful goal setting. Table 28.1 lists basic rehabilitation strategies and more experimental ones that may find a role, depending on the targeted impairment of the novel repair approach. When applied to participants in near future trials of neurorestoration, some of these methods are likely to interact iteratively with molecular, cellular, and pharmacological approaches to help activate or disinhibit a relevant neural network, alter the molecular milieu to better enable regeneration and synaptogenesis, and help sculpt selective recovery of movement. Thus, it is not enough to simply record whether any physical, occupational, or language/cognitive therapy was provided and its duration. Leaving the type, intensity, and duration of therapy open-ended and uncontrolled may introduce noise that a covariate statistical method cannot correct. Therapy ought to be standardized and optimized to improve targeted sensorimotor outcomes in the experimental and control arms of a trial.

Strengthening and Aerobic Fitness Exercise

Exercise has many effects on genes and molecular cascades that have been associated with learning, memory, and regeneration [19, 20]. Deconditioning and disuse muscle weakness can impede functional activities. A baseline level of aerobic and strengthening exercises ought to accompany biological interventions in highly impaired participants. Isometric, eccentric, and concentric exercise can be used to strengthen muscle groups that may contribute to a newly organized movement. Even a modest increase in agonist or antagonist power may enable a newly evolving movement to reach a clinical threshold, if the biological intervention is successful.

Table 28.1 Rehabilitation approaches for trials that can be combined to augment biological strategies to regain motor control of upper or lower extremities after stroke, TBI, and SCI

Basic strategies
Coordinated, multidisciplinary rehabilitation team care
Progressive intensive practice
Targeted impairment-related practice
Targeted task-oriented practice
Constraint-induced movement therapy practice protocol
Over-ground training of walking and balance with corrections for temporospatial, kinematic, and kinetic deviations
Body weight-supported treadmill training
Exercise for general strengthening and fitness
Walking aids, splints, orthotics
Cognitive training for impairments in sensorimotor integration, attention, working memory, and executive function
Wearable sensor-derived feedback about type, quantity, and quality of exercise and skills practice; motion algorithms to remotely monitor practice
Smartphone cueing to encourage practice sessions
Tele-rehabilitation to monitor and progress home-based practice and functional changes
Possibly useful strategies
Action observation; mental practice by motor imagery
Bimanual UE practice
Biofeedback of force, direction, angle, and speed of movements
Brain–machine interfaces to augment network feedback in training
Electrical stimulation with or without EMG feedback of targeted muscle groups
Electromechanical or passively supportive exoskeletal assists
Functional electrical stimulation of components of sought movement
Neural prostheses to enable training
Noninvasive brain stimulation (NIBS) of a specific network during practice
Transcranial magnetic stimulation
Transcranial direct current stimulation
Peripheral nerve and somatosensory stimulation
Pharmacologic modulation of neurotransmitters and learning modulators
Robotic-assisted movement training with feedback
Spinal cord electrical stimulation to lower the excitability threshold of motor pools
Virtual reality computer and immersive training environments

Task-Oriented Training

Progressively challenging practice of selective voluntary movements, initially supported by a therapist or caregiver, can lessen moderate chronic impairments and disability, as well as contribute to gains early after injury [21]. Practice ought to be goal-oriented and relevant to personal goals for skills retraining. In general, no one therapy listed in Table 28.1 is clearly better than another, but many have revealed efficacy compared to no specific intervention. For example,

constraint-induced movement therapy (CIMT) has received much attention. 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 [22]. Candidates for CIMT, however, must already have at least 10° of wrist and finger extension, which suggests a fair level of motor control. Without some wrist and hand function and ability to reach, constraint of the unaffected hand would not be feasible at home. The value of the intervention is that it includes a range of progressively difficult UE practice movements across single and multiple joints and real-world tasks, in keeping with other task-related, repetitive practice paradigms for motor skills learning. However, even 2 h of progressively challenging therapy with little or no constraint also seems better than less focused UE therapy [23].

Splints and orthotics may better position a joint so that newly acquired movements can be practiced and made more functional. For example, an orthotic that slightly extended the paretic wrist might enable active pinching if modest finger extension and flexion recovered. For a trial of a biological approach, the investigators ought to specify what orthotic was needed and what function was gained by making it available.

Robotic-Assisted Upper Extremity Training

Some cleverly designed electromechanical-assistive devices such as shoulder–elbow–wrist controllers have undergone clinical trial testing. The results, in general, especially for highly impaired participants after stroke and SCI, are generally not better than more conventional training techniques [24, 25]. The Veterans' Administration's upper extremity robotics trial offers some insight into expected outcomes for highly impaired hemiplegic persons [26]. The entry criteria was moderate to severe motor impairment, defined as a score of 7–38 on the Fugl-Meyer Motor Assessment of an upper limb from a stroke that had occurred at least 6 months before enrollment. At 12 weeks, the mean Fugl-Meyer score for patients receiving robot-assisted therapy was better than that for patients receiving usual care, meaning no intervention, by 2.17 points and worse than that for patients receiving intensive conventional rehabilitation by −0.14 points, but the differences are rather trivial and not statistically significant. This study may represent the maximum gain for an UE skills training protocol for the types of patients likely to be tested with cellular therapies, at least that can be measured by the Fugl-Meyer, which looks at a series of synergistic and more selective movements, However, the use of such robotic devices for Phase II and III trials of novel biological interventions could enable a reproducible rehabilitation strategy for highly impaired participants.

Mobility Training

Early biological trials are likely to include the goal of reciprocal leg movements and balance for walking after stroke and SCI. Participants at time of entry are likely to be unable to flex at the hip or extend the lower leg against gravity [27–29]. Progressive practice over ground includes selective muscle strengthening, building endurance, and physical and verbal cues to improve spatiotemporal, kinematic, and kinetic aspects of reciprocal leg movements and balance for walking. Goals include aiming to lessen asymmetries between the legs in single-limb stance and swing duration, and increase stride length, speed, and distance walked with or without passive assistive devices. These goals have been addressed, along with enhancing fitness, using body weight-supported treadmill training and robotic-assistive electromechanical devices. The results suggest that these interventions do not improve walking-related outcomes more than conventional gait training over ground of equal intensity after disabling stroke [30], SCI [31, 32], or TBI, but these strategies may enable step training and trunk strengthening in highly impaired subjects to facilitate the potential effects of a biological approach [33]. Intelligent exoskeletons for walking practice may also serve as training devices—several commercial ones are now available to enable stepping over ground.

Noninvasive Brain Stimulation

Much recent research has examined the potential for transcranial direct current stimulation (tDCS) [34] and repetitive transcranial magnetic stimulation (rTMS) [35] to improve motor function after stroke, especially for UE and swallowing movements. The data suggest that the best results come from a combination of targeted practice during the time of brain stimulation, which may unmask latent pathways, strengthen residual and new connections, modulate neural oscillations, and potentially increase functional connectivity [36]. However, the modest gains found so far apply only to patients with mild to moderate motor impairments.

Repetitive TMS studies to date use highly variable stimulation protocols and assessments of outcomes. If rTMS is used to try to augment biological repair along with rehabilitation, further experimentation will be necessary to determine whether to directly excite ipsilesional primary motor cortex (M1) or another motor-associated region; indirectly excite ipsilesional M1 by suppression of contralateral M1; optimize the type and frequency of stimulation such as theta burst, 1 or 5 Hz stimulation which have very different short-term physiological effects; carry out a simple attentional or targeted muscle contraction [37] or a more skilled task during and for a short time after the stimulation protocol; understand what aspects of a movement may benefit from any sort of stimulation; optimize the number and schedule of bouts of stimulation plus therapy; or continue to train beyond the time of stimulation. For some repair strategies, rTMS and tDCS may be able to augment descending drive to uncrossed and recrossing corticospinal and other supraspinal axons that

activate motor pools for selective and combinational movements. It is most intriguing that cortical electrical stimulation may increase sprouting of the unaffected corticospinal tract onto the ipsilesional ventral horn of the spinal cord [38].

Other CNS and PNS Stimulation Adjuncts

Other electrical means to increase excitability of latent residual pathways may be of interest in biological trials. Methods include continuous deep brain, direct spinal cord, and peripheral nerve stimulation during practice [39]. Deep brain stimulation to date is probably too invasive to serve as an adjunct—methods to modulate neural oscillations would have to be shown to be efficacious by independent trials. A single-subject design of spinal cord stimulation in motor complete paraplegic participants enabled modest voluntary leg movements, sometimes against gravity. Perhaps the stimulation lowered the threshold for motor neuron excitability by latent supraspinal inputs to them [40]. This does not imply that the subjects would be able to walk, however. But if a less invasive stimulation intervention proved feasible and reproduced such findings, then it might augment the use of biological approaches to provide circuit specificity for further training. Pairing TMS with peripheral nerve stimulation and dual bihemisphere TMS may also selectively increase cortical network excitability to augment training, but efficacy studies are pending.

Brain–Machine Interfaces

A brain–machine interface (BMI) [41] for rehabilitation uses an analysis of various types of brain signals from imagining a movement to direct the desired movements of, for example, a robotic arm. This training may augment synaptic efficacy for the actions performed and drive latent pathways that can come to be involved in solving the movement problem. Early studies suggest that practice, combined with cortically implanted electrodes and robust movement-associated algorithms, can improve motor control, leading to improvements in functional connectivity of motor-related pathways [42]. Affordable, safe, and efficacious complete systems for rehabilitation to try to improve motor control of a plegic limb might complement an intervention for neural repair.

Other Possibly Complementary Interventions

Electromyographic feedback from a minimal voluntary muscle contraction that then triggers functional electrical stimulation to increase the contraction has improved the voluntary control of single muscle groups and may be useful when the repair strategy aims to increase supraspinal control of that muscle [43]. This may be most applicable to the patient with a cervical SCI who is trying to regain motor control

1–2 levels below the lesion or in the hemiplegic patient trying to regain wrist or finger extension.

Many other techniques may serve to help engage, activate, and reinforce a neural network to focus neural resources on accomplishing a sensorimotor task. Training in a virtual reality environment, using imagery of a task as a form of practice, and UE mirror therapy have been of some benefit in patients with fair motor control [44–46]. All increase activation of M1 and other cortical and subcortical motor network nodes [47]. These are potential adjuncts for biological approaches, but may be difficult to incorporate into Phase II or III trial designs because they add complexity.

Pharmacologic Agents

Medications developed for other uses, especially ones that may act as neurotransmitters and on attention, have a long history of being tried for stroke and TBI. None so far have enough evidence behind them to warrant use as an adjunct in a repair trial. The most likely to be considered would be fluoxetine [48], reboxetine [49], and amantadine, but not dopamine agonists [50]. For cognitive and behavioral outcomes, modest if any benefits are apparent for cholinergic and catecholinergic drugs that might also impact motor control [51].

Tele-rehabilitation

The field of mobile and wireless health (mHealth) [52] offers ways to monitor, remotely and inexpensively, the activities of participants in trials. Wearable wireless sensors, such as accelerometers and gyroscopes, can recognize the type, quantity, and quality of walking, cycling, running, leg exercises, and other nonsedentary behaviors by fusing signals from the legs and analyzing them with pattern recognition algorithms [53]. Thus, it should be feasible to monitor how much and how well a trial participant is practicing a rehabilitation strategy, give verbal or text feedback about performance over a smartphone, and collect interim ratio scale measures relevant to outcomes and adverse responses. This scenario may enable more subjects from remote geographical regions to conveniently enter trials and limit the burden of repeated clinic visits. Serial monitoring and objective sensor-based annotation of targeted movements may also enable investigators to better discern between restoration versus substitution versus compensation within changes in functional movement goals [54].

Combinational Strategies

The combination of a molecular, cellular, or novel pharmacological approach with targeted rehabilitation would seem likely to augment each other and increase the likelihood of more robust outcomes. This is one of many enrichment strategies for

Phase II and III trials [55]. Is there a cost-effective way to interleave rehabilitation with a biological approach during a randomized clinical trial?

The STEPS participants recommended that cellular therapy trials should include at least two pretreatment baseline examinations to assure a stable baseline in a homogeneous group of subjects [56]. For trials that start in a late subacute or chronic period after injury onset, however, spontaneous degradation of function may have intervened or latent function may not be brought out by the neurological examination. One solution is to phase in therapy for targeted improvements for 10–12 sessions for 2 h each over 2–4 weeks, focused on, for example, UE motor activities, emphasizing the shaping and progressive practice procedures used in the EXCITE trial [55]. This training might include the use of a resistance stretch band for strengthening exercises, if feasible. If the repeated neurologic examination and primary outcome measurements are stable, the investigators can proceed with the biological intervention with greater confidence that any gains can be attributed to the experimental intervention. Concern about forced or early high levels of exercise has been raised by studies in animal models [57]. However, this may be more of an issue within the first 3–7 days after onset of injury in animal models, rather than in clinical trials, where intensive exercise falls far below what mice and rats can be induced to do.

A phase-in of therapy also reinforces how to practice. Further practice can be accomplished at home using wearable sensors or a tele-rehabilitation protocol to encourage and monitor practice. Every 1–2 weeks, a centrally located therapist can watch the subject at practice using a smartphone or tablet camera, review summarized sensor data about daily activity, and make suggestions about how to continue. Possible advantages to this scenario are that the trialists will annotate the therapy actually received, improve reliability of procedures, develop dose–response information regarding motor changes over time, maximize the interaction between the biological intervention and rehabilitation, and generally increase the validity of the trial. This strategy may also provide the basis to improve future trial designs as well as test new sensor-based outcome measurement tools.

Outcomes

The STEPS participants suggested the potential use of modality-specific outcome measures, tested in a Phase II design and possibly serving as the primary outcome in a Phase III cellular trial [56]. This approach could lead to a modality-specific FDA label for the approach, but that may be fine for a study of motor recovery [58].

The combination of a biological approach with targeted rehabilitation lends itself to developing the outcome measures that are most likely to be driven by the combination. What is practiced should have a close relationship to the primary outcome measurement. Rehabilitation plus repair also represents a complex intervention. For trials, the investigators will want complex outcome measures, so they can detect (1) any biological activity of the repair intervention; (2) change in impairment;

(3) any clinically meaningful increase in daily functioning and participation in relevant activities; and (4) self-reported change in quality of life for better or worse. Biomarkers of repair such as functional, connectivity, and structural MRI and perhaps TMS for changes in cortically elicited motor evoked potentials may provide other ways to detect motor responses to the interventions.

Many of the varied symptoms, impairments, and functional activities of patients may change to differing degrees over the course of a biological intervention. It is costly and a burden on participants to try to measure everything, looking for a sign of improvement in neural functioning. If a nonmotor outcome is of interest, however, a baseline level of function will be necessary. For example, if improved bladder control is a possibility, i.e., continence, voluntary voiding, no retention, etc., then several weeks of measures of urine frequency and post-void residual volumes are needed as a measurement tool for comparison in a secondary analysis. After a high SCI, if dysautonomia is targeted, then delete, prebiological therapy for blood pressure and heart rate, spasms, and bouts of dysreflexia, as well as symptoms, must be serially monitored for several weeks before and after the treatment.

NIH-funded trials ought to include standard measures that allow comparisons across trials, such as those described in the NIH Toolbox. But the FDA and biotechnology companies ought to consider the likelihood that such tools may not capture the proof of principle about whether a cellular intervention modulated biological activity in ways that fell below the sensitivity of those standard tools. Consider the ordinal-scaled stroke tools, such as the NIH Stroke Scale, modified Rankin Scale, and Fugl-Meyer Motor Assessment. The NIHSS looks only at gross sensorimotor impairment. The Rankin emphasizes walking ability with a mix of impairment and disability categories, but does not provide any standard way to assess the details of motor functions and motor- or cognitive-related disability. The Fugl-Meyer assesses limb movements in and out of upper motor neuron synergies. The scale cannot assess more subtle single joint motor changes, so it is generally not a targeted outcome measure. Another commonly employed tool is the American Spinal Injury Association AIS Impairment Scale for sensorimotor testing. Only one muscle is tested for each of the C4–T1 and L2–S1 root innervations, so changes in other groups may go undetected. TBI measures tend to underemphasize functional movements in favor of cognitive and participation scales. Phase II trials could include potentially more sensitive outcome measurements that are specific to anticipated motor changes, as well as assess-related functional gains (Table 28.2).

Table 28.2 Protocol for weaving a cellular, molecular, or novel pharmacological intervention with rehabilitation for a motor deficit

1.	Initiate a rehabilitation strategy that is relevant to the anticipated outcomes for the biological intervention
2.	Continue until a stable within-subject baseline is achieved for anticipated motor outcomes
3.	Initiate the biological intervention
4.	Depending on preclinical and prior clinical dose–response studies, restart a similar progressive rehabilitation strategy within the best timeframe in both experimental and control groups
5.	Serially measure the primary outcomes for the biological and rehabilitation interventions that are being studied

Motor assessments might include testing 3–4 muscle groups from each root level for the arm and leg, using the British Medical Council Scale. Where voluntary movement was ≤3/5 before the intervention, the joint should be positioned on a fixed surface to detect new degrees of movement. Surface electromyography and wireless sensors such as accelerometers, gyroscopes, and goniometers may be applicable as monitoring tools for newly organized movements. Scales such as the Fugl-Meyer for selective multijoint movements would supplement the targeted decrease in motor impairment, as would timed tasks and functional scales that were relevant to the goals of the rehabilitation plus biological approach.

Conclusion

In testing molecular, cellular, and novel pharmacological restorative approaches, rehabilitation skills training should aim to optimize improvements in targeted sensorimotor outcomes, as well as other goals for impairment, disability, and participation. This dual strategy may selectively activate neural networks to optimize connectivity, learning, and memory. Outcome measurement tools need to be sensitive enough to describe and quantify newly induced improvements.

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