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Rehabilitation After Stroke: Current State of the Science

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Abstract

Stroke rehabilitation is evolving into a clinical field based on the neuroscience of recovery and restoration. There has been substantial growth in the number and quality of clinical trials performed. Much effort now is directed toward motor restoration and is being led by trials of constraint-induced movement therapy. Although the results do not necessarily support that constraint-induced movement therapy is superior to other training methods, this treatment has become an important vehicle for developing clinical trial methods and studying the physiology underlying activity-based rehabilitation strategies. Other promising interventions include robotic therapy delivery, magnetic and electrical cortical stimulation, visualization, and constraint-driven aphasia therapies. Amphetamine has not been demonstrated to be effective, and studies of other pharmacologic agents are still preliminary. Future studies will incorporate refinements in clinical trial methods and improved activity- and technology-based interventions.

Keywords

Rehabilitation; Clinical trials; Cerebrovascular disease; Recovery

Introduction

In the past two decades, stroke rehabilitation has evolved from a field dominated by expert opinion and clinical tradition to one focused on exploiting recent advances in the neuroscience of development, physiology, imaging, and cognition. Many laboratory findings have progressed to preliminary and small-scale studies testing the relevance and utility of these interventions in the clinical setting. Now large-scale phase 2 studies are commonplace, and the first cohort of phase 3 rehabilitation trials is entering the literature. See Table 1 for a list of some of the largest clinical trials that are ongoing at the time of this writing.

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By far, the strongest focus in rehabilitation research has been on motor restoration of hemiplegic limbs, perhaps the most obvious and disabling consequence of stroke and one particularly accessible to imaging and physiologic investigation. However, substantial work in aphasia remediation, hemispatial neglect, pharmacotherapy, and biomechanics also has been done. In this article, we critically review important findings from this area and place these findings in the context of current clinical practice and future research directions.

Constraint-induced Movement Therapy

Constraint-induced movement therapy (CIMT) emerged from 19th century primate models of deafferentation and was developed as a clinical intervention by Taub and Uswatte [1], Wolf et al. [2], and others. It has two major components: restraint of the less affected upper extremity (UE) and training of the hemiplegic UE using a shaping paradigm. Shaping consists of practice of skilled tasks calibrated to the patient's motor capacity, advancement of task difficulty as the patient improves, and generous feedback and encouragement.

In terms of effect size, CIMT leads other therapies for arm motor restoration, with a standardized mean difference of +0.73 for arm function (moderate size effect is defined as +0.5) in a recent meta-analysis [3]. An important multisite randomized controlled trial (RCT) of CIMT in chronic stroke patients (EXCITE [Extremity Constraint Induced Therapy Evaluation]) showed improved dexterity and self-reported UE use in the CIMT-treated group, which were maintained up to 24 months after treatment [4••]. These results and others have led to the development of CIMT clinical programs and efforts to obtain third-party payment.

Yet although CIMT is effective, its superiority over other training methods remains unproven. The EXCITE trial design used a usual and customary treatment control, which in the United States means the control group received little or no therapy. Thus, simple dosage effects rather than a superiority of CIMT might explain the EXCITE result. Smaller studies that do control for the number of hours of active motor training have not shown CIMT to be consistently more effective than other treatments [5•,6]; however, those studies differ in time after stroke, subgroup analyses, and other features.

Attention is turning to using CIMT to identify the key determinants of treatment response in motor training. The likeliest “active ingredients” are the dose of activity, the timing of the treatment, and the constraint. In an activity-based intervention, dose is most commonly quantified by the amount of time spent, the number of movements attempted, or the perceived effort. A secondary analysis of EXCITE trial data found no relationship between CIMT intensity and improved Wolf Motor Function Test scores, except in a specific subgroup of uncertain clinical relevance [7]. Results from the recent VECTORS (Very Early Constraint-Induced Movement During Stroke Rehabilitation) trial have challenged the assumption that more therapy is always better [5•]. In VECTORS, 52 stroke patients were randomly assigned to receive CIMT, equivalent-dose standard therapy, or high-dose CIMT. The results showed no difference between the CIMT and equivalent-dose standard therapy groups in functional limitation at 90 days. Surprisingly, the high-dose CIMT group exhibited significantly less improvement than the other groups, demonstrating the importance of developing dose-response relationships for all neurorehabilitation interventions.

Time after stroke onset also may be important; rodent models of stroke recovery suggest that windows of opportunity exist after stroke onset [8]. Most positive CIMT trials were performed in chronic stroke patients, but when CIMT is administered at the acute and subacute stages, results are more equivocal, with some studies showing no difference between CIMT and control groups at 3-month follow-up [6]. Furthermore, VECTORS showed that high-dose CIMT (3 h shaping/day) during the early stage may result in even less recovery.

Is it the constraint itself? Recent research on interhemispheric interactions support the notion that pronounced reciprocal interhemispheric inhibition is present at baseline and that after stroke, the unaffected hemisphere exerts unopposed inhibition on the damaged hemisphere, impeding recovery. Limb constraint may exert its effect by decreasing activity in the unaffected sensorimotor cortex, thereby decreasing inhibition on the affected hemisphere. Yet, some studies question the need for any constraint. In a study of shaping without constraint, improvement in the treatment group was found in six elements of the Wolf Motor Function Test [9].

Above all, these CIMT studies demonstrate the need to directly address timing, dose, patient population, and treatment fidelity. Regardless of the intervention in question, these issues will be prominent in the next generation of trials. Current studies of CIMT are incorporating brain mapping techniques such as functional MRI and transcranial magnetic stimulation (TMS) to identify neural correlates of behavioral effects. Thus, CIMT is an important vehicle in developing a neuroscientific perspective on how activity-based therapies engage mechanisms of brain plasticity, modulate cortical excitability, and affect cortical motor maps. Taking these processes into account will be essential in developing the next generation of theory-driven interventions.

Approaches to Gait Retraining

Hemiparetic stroke survivors want to walk. Although regaining strength may seem paramount, the latest RCT of the effects of functional strength training versus conventional physiotherapy concluded that leg strengthening has no effect on walking speed, at least in persons with some walking capacity [10]. Even as an adjunct, the added benefit of focused strength training is not clear [11].

Body weight support treadmill training (BWSTT) has received much attention because it facilitates massed practice of gait and allow patients to focus on more normal gait biomechanics. However, a recent single-blind RCT of 97 subacute nonambulatory stroke patients found no difference when one third of the gait training provided was BWSTT [12]. Compared with a control group that received only conventional therapy, no differences were found in any measure immediately after treatment or at follow-up, consistent with much of the recent BWSTT literature. Multicenter trials are ongoing (Table 1).

Further advances in motor rehabilitation likely will be contingent on a better understanding of the processes involved in motor learning. Motor adaptation can be harnessed using a split-belt treadmill (one belt fast, the other slow) to transiently reverse the gait asymmetry characteristically seen after stroke [13]. Strokes involving the basal ganglia may lead to specific deficits in motor memory, sequencing, and planning [14]. Certain aspects of motor learning may depend on proper sleep, especially when studied in stroke patients [15]. These types of findings and others in motivation, attention, and self-efficacy might affect future rehabilitation strategies.

Rehabilitation Robotics

The task-specific repetitions performed in conventional rehabilitation are shockingly few compared with those required to engage neural plasticity in models of animal and human motor learning [16••]. One solution may be the application of rehabilitation robots to achieve many more repetitions. A variety of UE robotic systems have been developed, including the MIT-Manus, Mirror Image Movement Enabler, Bi-Manu-Track (Reha-Stim

Co., Berlin, Germany), Hand Wrist Assistive Rehabilitation Device [17], and NeReBot (Mechatronics, Padova, Italy) among others. At this time, robot-assisted UE therapy appears to be at least as effective [18], if not more effective [19], than dose-matched conventional therapy both early and late after stroke.

For gait retraining, devices such as the Lokomat (Hocoma, Rockland, MA), which consists of a treadmill, support harness, and computer-driven gait orthosis for each leg, are increasingly popular. Two recent trials found that conventional-therapy controls had a larger increase than the Lokomat-trained group in their gait speed [20,21••]. These surprising results contradicted observations from nonambulatory stroke patients [22], but there were several design differences. Robots may impose constraints that limit the degrees of freedom of movement and decrease error signal that may be essential for motor learning to occur [21••].

Virtual Reality, Mirror Therapy, and Mental Imagery

Virtual reality (VR) has potential advantages: it can provide massed practice of a skill with many repetitions, task practice can be finely manipulated and made engaging, and sensory input can be controlled. Research in this area is still in the early stages, and studies often are underpowered and lack controls. There have been no direct comparisons of immersive VR with conventional rehabilitation.

In mirror therapy (MT), the reflection of the moving unaffected limb is superimposed on the affected limb, creating the illusion of movement in the affected limb. Originally used as a treatment for phantom limb pain, MT now is applied to hemiplegia. As an adjunctive therapy, it is associated with lasting improvement in UE function [23•] and has shown promise for severe distal plegia [24]. However, little is known about the mechanism of MT in stroke. Preliminary results from a study using VR to simulate MT showed increased activation and excitability of the ipsilesional sensorimotor cortex in response to the movement of the unaffected hand [25]. These intriguing findings await replication.

Might we dispense with robots, VR, mirrors, and other gadgets entirely? The long-held impression that mental imagery can improve motor performance received scientific support recently, as Page et al. [26] reported that therapist-guided adjunctive mental practice was associated with increased dexterity and changes in patterns of cortical activation. RCTs are ongoing (Table 1).

Cortical Stimulation and Brain Mapping

The EVEREST trial comparing rehabilitation alone with rehabilitation and concurrent cortical stimulation using subdural electrodes produced a disappointing result. Although direct brain stimulation enhanced the effects of activity-based rehabilitation in animal and preliminary human trials, this phase 3 study with 146 patients detected no difference in UE impairment or dexterity [27•].

Despite EVEREST, TMS and transcranial direct-current stimulation (tDCS) have significant potential. In TMS, a rapidly changing magnetic field at the surface of the scalp is used to create small currents that transiently disrupt neuronal activity in the underlying cortex. Depending on the timing and frequency of these pulses, long-lasting inhibitory or facilitatory effects on cortical function may be observed. One application of TMS is inhibition of the unaffected hemisphere. Because of the removal of normal interhemispheric inhibition, this method transiently improves functioning of the lesioned hemisphere and has been associated with improved UE dexterity [28••]. tDCS uses a very low-intensity current to create regional brain polarization that modulates cortical excitability. Paired with peripheral nerve stimulation, tDCS is associated with improved performance on a motor sequence task in chronic hemiparesis [29].

Brain mapping also is providing useful insight into mechanisms, and it is widely hoped it will support “prescriptive” interventions, that is, specific interventions for specific lesions. Corticospinal tract integrity measured by diffusion tensor imaging correlates with motor performance and arm motor function [30•]. Functional connectivity MRI, which measures synchronized spontaneous fluctuations in activity in regions of the motor network, demonstrates that motor performance depends on interhemispheric connectivity rather than ipsilesional connectivity in subacute stroke [31]. The early presence of TMS-induced motor-evoked potentials may serve as a prognostic indicator of recovery [30•]. Blood oxygen level–dependent (BOLD) functional MRI activations in the ipsilesional postcentral gyrus and cingulate cortex within the first 2 days of stroke are associated with better 3-month outcomes, possibly because of their role in new motor learning [32].

Rehabilitation for Aphasia and Neglect

As is the case with rehabilitation of motor function, research on aphasia rehabilitation in the past few years has been dominated by constraint approaches. In constraint-induced language therapy (CILT), patients with aphasia undergo an intense treatment program relying solely on verbal communication; no other means of communication (eg, gesture or writing) are permitted. In fact, barriers are erected between patient and communication partner to prevent other communication exchanges from taking place. Hallmarks of this treatment are that verbal communication is required and treatment is intense. Studies typically include 2 to 3 h of therapy per day, every day, for a 2-week period. CILT studies in chronic aphasia have all reported improvements in language impairment after training [33].

In a recent systematic review, Cherney et al. [34•] examined the effects of both intensity alone and CILT in 10 studies. In five studies examining intensity of treatment, more intense training produced greater changes in language impairment than less intense training in both the acute and chronic phases. Interestingly, studies that also included measures of language change at the activity level produced mixed results; that is, some studies found more intense treatments improved discourse production or functional communication, whereas others found intensity had negative effects on functional language. An issue of note in this developing literature is that many studies both of intensity and of CILT comprised either a case series or single-subject design; few of these studies were controlled trials. Moreover, of the controlled trials, most had modest sample sizes, ranging from 9 to 27 participants.

Research on aphasia rehabilitation has moved beyond demonstrating that aphasia therapy is effective to determining factors critical to optimizing treatment gains. There have been several exciting developments in this regard. First, as stated earlier, treatment intensity is a critical variable in maximizing recovery [34•,35], although its mechanisms and consequences on functional ability are not fully understood. More intense treatments produced better outcomes on measures of impairment; what is unclear is whether those gains translate to functional communication in everyday settings and can be maintained over time. An important challenge for the rehabilitation community is that treatment, particularly outpatient treatment, is not typically delivered in a format that supports intense therapies. Patients are scheduled into hour-long treatment slots a few times per week over months. It will be difficult, although not impossible, to retool rehabilitation schedules to support more intense training. Second, cognitive factors have been examined to better determine which patients likely will benefit from particular treatment approaches. For instance, Nicholas et al. [36] reported that people with aphasia with concomitant deficits in executive abilities do not benefit as much from training with an augmentative communication system, despite having intact semantic abilities. These types of studies point out the importance of examining other cognitive factors as prognostic indicators of recovery. Third, time after onset was examined systematically to determine whether treatment benefits are limited to the acute phase of recovery. Moss and Nicholas [37] reported that benefit from treatment was not determined by time after onset. To the contrary, treatment initiated beyond 1 year after stroke resulted in a 28% to 47% change of the maximum possible, indicating that substantial improvements are possible in the chronic phase of recovery.

Two recent developments challenge classical thinking about language rehabilitation. First, Manheim et al. [38] reported success with computer-based script training in improving communication skills. Script training provides patients with extended home-based practice in personally relevant material through interaction with a computer avatar. Twenty participants with chronic aphasia practiced at home for 9 weeks, checking in weekly with a therapist to monitor practice and progress. Script training significantly reduced reported communication difficulties, challenging the currently held notion that treatment must proceed from more basic linguistic processes through to higher-order functions. Script training is noteworthy in two ways: 1) patients have more control over the target of therapy, and 2) their visits with the therapist are optimized. Therapists set up scripts, facilitate successes, and assist clients in overcoming challenges during one-on-one meetings, but clients execute extended practice at home.

In the second development, Kiran [39] designed a technique to treat naming deficits that calls into question prevailing clinical wisdom that patients should be trained on prototypical members of a category, such as *robin*, before tackling exceptions to the category, such as *penguin*. In fact, she convincingly demonstrated the opposite—namely, training prototypical members of a category produces no generalization to atypical members, whereas training atypical members produces transfer of training to prototypical members. This treatment approach represents a fundamental shift in thinking and will change the way naming therapies, and perhaps other therapies, are conducted henceforth.

In other realms of cognitive rehabilitation, few definitive clinical trials have been conducted over the past few years. Neglect treatment studies have continued to focus primarily on three techniques: prism adaptation, sensory stimulation, and VR training. Limited success with these techniques has been reported immediately after treatment [40], with little evidence that these changes persist over time. One small-scale study of VR training of street crossing, however, found that training transferred to improved skill in real-world street crossing [41].

A positive development in cognitive rehabilitation is a growing awareness of executive function deficits after stroke that not only have an impact on the rehabilitation process itself, but may translate to dysfunctions in daily life after discharge [42]. In addition, more holistic approaches to cognitive issues have begun to be studied. For example, a trial for patients with slowed information processing that compared Time Pressure Management (TPM) training with usual care produced reductions in complaints about mental slowness in both treatment groups, but found that TPM improved processing speed to a greater extent at 3 months [43]. Additionally, a trial of aerobic exercise versus stretching found greater benefits on processing speed and improved mobility for the aerobic exercise group, with the effects lasting only as long as the exercise program [44].

Other Stroke Rehabilitation Topics

Pharmacologic augmentation of recovery remains attractive, actively investigated, and elusive. Amphetamine continues to be the most thoroughly investigated agent, based on numerous rodent experiments showing that, when paired with task-specific activity, it can accelerate motor recovery. This finding led to the widespread clinical use of amphetamine and other stimulants. However, a recent large-scale phase 2 trial for motor recovery found no benefit [45]. Moreover, a new meta-analysis did not support amphetamine's effectiveness in motor recovery and raised issues about safety [46]. Recent pharmacologic adjuncts to aphasia therapy show modest promise [47,48]. No substantive data support the use of methyphenidate to augment motor recovery.

The hemiplegic shoulder pain syndrome is a disabling complication of stroke reported in 5% to 84% of stroke patients. Although UE weakness recently was reported to be an independent risk factor for hemiplegic shoulder pain, this syndrome likely has many causes, including shoulder joint capsulitis, complex regional pain syndrome, impingement of the supraspinatus ligament, and associated inflammation. A recent ultrasound study demonstrated frequent soft tissue injury within weeks of stroke onset [49], and a reproducible shoulder physical examination was developed to standardize clinical evaluation [50].

Clinically, range-of-motion exercises, resistance training, and positioning techniques are used most commonly, although few data support their efficacy. The evidence base is strongest for surface electrode electrical stimulation, but intramuscular electrode placement may have advantages that outweigh minor discomfort in placement and infection risk [51]. Subacromial corticosteroid injections and anti-spasticity treatments are used widely but lack a strong evidence base.

Conclusions

Whether the results have been positive or negative, the fact that there are rigorous rehabilitation trials to discuss is an enormous step forward in the development of more effective restorative treatments for stroke. Much effort is now devoted to building better trial methods and using emerging technologies to study the brain physiology underlying recovery and the response to rehabilitation interventions. The process of vetting these interventions already has provided evidence that studies that do not control for the timing, dose, and method of delivery must be interpreted with caution. In addition, future studies should make the most of brain mapping techniques such as functional MRI and TMS to identify the neural correlates of behavioral effects. These efforts will allow the development of more powerful treatments and the means to detect the effects of those improved treatments in a clinical trial. Combined with promising cellular and molecular interventions now being investigated in the laboratory, the future for hypothesis-driven, restorative treatments for stroke is bright.

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Table 1

Upcoming and ongoing phase 2 and 3 trials in stroke rehabilitation*

Study	Purpose	Design	Projected patient enrollment, *n*	Population	Interventions/control group(s)	Primary outcome measure(s)	Other comment(s)
Norwegian Constraint-Induced Therapy Multisite Trial (NORCIMT)	To compare CIMT in the early vs later phases of stroke recovery	Phase 3, treatment, randomized, single-blind, parallel assignment, efficacy study	120	Early subacute (<26 d post stroke)	Early intervention: modified CI therapy starting between 7 and 28 d post stroke Delayed intervention: modified CI therapy starting 6 mo post stroke	Wolf Motor Function Test	Modified CI therapy: 10 treatment days 3 h/d —shaping exercises, 2 h; task practice, 0.5 h; behavioral therapy (transfer package), 0.5 h. Wearing of restraining mitt encouraged but not controlled.
Locomotor Experience Applied Post Stroke Trial (LEAPS)	To evaluate gait retraining	Phase 3, multicenter, treatment, randomized, open-label trial	400	Subacute	Early locomotor: BWSTT Late locomotor (6 mo post stroke): physical therapist-monitored exercise program Early home exercise (2 mo post stroke): nonspecific low-intensity exercise program	Gait speed	12-mo follow-up
Interdisciplinary Study of Arm Rehabilitation After Stroke (ICARE)	To compare an experimental arm therapy, the ASAP, with 2 standard types of therapy	Phase 3, interventional, treatment, randomized, single-blind, active control, parallel assignment, efficacy study	360	Subacute (<75 d post stroke)	ASAP Dose-equivalent UCC UCC	Wolf Motor Function Test Stroke Impact Scale	12-mo follow up In ASAP, participant chooses his/her own challenging and meaningful activities
Assisted Movement Neuro-rehabilitation: VA Multi-site Clinical Trial	To compare the effectiveness of lower-dose and higher-dose robotic limb therapy with MIME device	Phase 3, treatment, randomized, double-blind, dose comparison, parallel assignment, efficacy study; multisite	50	–	Low-dose: 1 h/d mechanically assisted upper limb movement + traditional therapy High-dose: 2 h/d mechanically assisted upper limb movement + traditional therapy Traditional therapy	Fugl-Meyer score	–
Sub-Acute Stroke Rehabilitation With AMES	To determine whether use of the AMES device can increase the amount of motor recovery in disabled stroke subjects during	Phase 3, treatment, randomized, double-blind, placebo-control, crossover assignment, efficacy study	156	Subacute (<4 mo post stroke)	18 half-hour AMES sessions per qualified subject limb Sham Crossover group receiving AMES	Fugl-Meyer score	–

Study	Purpose	Design	Projected patient enrollment, *n*	Population	Interventions/control group(s)	Primary outcome measure(s)	Other comment(s)
	the subacute period						
Non-invasive Brain Stimulation and Occupational Therapy to Enhance Stroke Recovery	To investigate whether tDCS can enhance the effects of occupational therapy	Phase 3, interventional treatment, randomized, double-blind, placebo-control, parallel assignment, efficacy study	80	Chronic (>6 mo post stroke)	Real tDCS + occupational therapy Sham tDCS + occupational therapy	3 J-ROM Fugl-Meyer assessment of upper-extremity motor impairment	–
Enhancing the Response to Rehabilitation After Stroke Using rTMS	To determine whether stimulation of the movement area of the brain just before arm and hand training improves performance	Phase 2, treatment, randomized, double-blind, placebo-control, parallel assignment, efficacy study	34	Chronic (>3 mo post stroke)	Experimental: real rTMS Sham comparator: sham rTMS	Box and Block Test of manual dexterity	For real rTMS, 1200 pulses were delivered at a frequency of 1 Hz and an intensity 115% of the baseline motor threshold For placebo, a sham coil was used. 20-min real and sham stimulation sessions were administered biweekly for 4 wk
Comparison of Embedded and Added Motor Imagery Training in Patients After Stroke	To compare the effects of integrated vs massed mental imagery on motor performance	Phase 2, treatment, randomized, single-blind, parallel assignment, efficacy study	90	3 mo post stroke	MI training included in 45 min of physiotherapy, 3 times/ wk for 2 wk 15 min of MI training added to a 30-min physiotherapy session, 3 times/wk for 2 wk 15-min control intervention added to a 30-min physiotherapy session, 3 times/ wk for 2 wk	Time in seconds to perform a motor task: going down, lying on the floor, and getting up again	–
Virtual Reality Training Program for Ambulatory Patients With Chronic Gait Deficits After Stroke	To study the feasibility and efficacy of VR systems to promote gait recovery after mild to moderate stroke in an environment in which components can be controlled and monitored	Phase 2, treatment, randomized, open-label, parallel assignment	48	Chronic	VR training for a total of 18 sessions (2/wk) + usual care Usual care	Community ambulation using step activity monitor; body sway-displacement; timed up and go; gait analysis	VR generated by CAREN Integrated Reality System[†]

[*] Data are summarized from Clinicaltrials.gov and strokecenter.org; therefore, they are only as accurate as the information posted on those websites.

[†] Manufactured by MOTEK BV, Amsterdam, Netherlands.

3J-ROM three-joint range of motion; *AMES* assisted movement with enhanced sensation; *ASAP* Accelerated Skill Acquisition Program; *BWSTT* body weight support treadmill training; *CI* constraint-induced; *CIMT* constraint-induced movement therapy; *MI* motor imagery; *MIME* mirror-image movement enabler; *rTMS* repetitive transcranial magnetic stimulation; *tDCS* transcranial direct current stimulation; *UCC* usual and customary care; *VR* virtual reality.