Title
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Journal
Stroke, 49(12)

ISSN
0039-2499

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Publication Date
2018-12-01

DOI
10.1161/strokeaha.118.021359

New Directions in Treatments Targeting Stroke Recovery

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Stroke is the leading cause of neurological disability in the United States and worldwide. Remarkable advances have been made over the past 20 years in acute vascular treatments to reduce infarct size and improve neurological outcome. Substantially, less progress has been made in treatments to enhance neurological recovery after stroke. However, several promising research directions have been identified for treatments targeting stroke recovery and are the focus of the current review (Figure).

Epochs of time poststroke can be divided into acute (hours-days), subacute (days-weeks), and chronic (months-years) based on the tissue response and biological programs that emerge during these time windows.[1] In contrast to acute stroke treatments, such as tPA (tissue-type plasminogen activator) and thrombectomy, for which the target is a clot, and where the goal is to salvage threatened brain tissue to limit injury, recovery treatments target surviving neural tissue with the goal of promoting neural repair.

Recovery trials are thus fundamentally different from acute stroke trials.[2] First, the time windows available for administering recovery-based treatments span much longer periods. These time windows enable detailed within-subject analyses before, during, and after treatment. Second, stroke deficits are multimodal (eg, combinations of motor, language, and other deficits) and recovery is modality-specific, meaning that different deficits recover with different rates and extents.[3] Accordingly, recovery trials often use modality-specific end points (such as the Fugl-Meyer [FM] Motor Scale), in addition to global outcome measures (such as the modified Rankin Scale [mRS] or the National Institutes of Health Stroke Scale [NIHSS]) that lump together all aspects of neurological function and are used in acute stroke trials. Third, recovery trials have issues often not shared with other stroke research domains, such as variable standards of care, patient access and retention, difficulty with experimental blinding (particularly in the study of behavioral interventions), and importance of concomitant experiences[4] (Table).

Spontaneous behavioral recovery occurs after stroke but is variable. The molecular and cellular mechanisms of this recovery have been extensively reviewed. Several treatment approaches in clinical translation aim to improve stroke recovery. Here, we review contemporary approaches to therapeutically enhancing stroke recovery, focusing on recent trials. For this review, we define stroke recovery treatments as nonvascular treatments initiated in the subacute to chronic phases (days to years) after stroke. Our intent is not to be comprehensive, but to highlight select examples of promising approaches and directions with an acknowledged emphasis on motor recovery. It should be noted that to date no small molecule or biologic has been approved by the Food and Drug Administration to promote stroke recovery.

Conventional Therapies

Conventional therapies for patients recovering from stroke include physical, occupational, and speech therapy. These are delivered across numerous care settings. The duration, intensity, and type of conventional therapy are highly variable in the United States, complicating the design of control groups in stroke rehabilitation trials. Indeed, one of the research priorities for stroke rehabilitation and recovery is better reporting and standardization of usual care in trials.[1]

Two specific interventions for stroke recovery with promising initial evidence emerging from conventional therapies include mirror therapy and constraint-induced movement therapy (CIMT).[5] Mirror therapy, or prism adaptation therapy, uses simple equipment to focus a patient's attention on a neglected hemifield. Mirror therapy, generally provided as an adjunct to conventional therapy, can improve motor function and reduce pain[6] and might improve activities of daily living.[7] Mirror therapy studies have been limited by small sample sizes and methodological limitations. Larger, more rigorous trials are needed. CIMT involves intensive rehabilitation therapy to overcome learned disuse by an affected arm, with concomitant constraint of the unaffected arm. EXCITE (Extremity Constraint Induced Therapy Evaluation)[8] was a phase 3 trial that found evidence that CIMT improved motor function, surpassing the minimally clinically important difference (MCID) in the Wolf Motor Function Test among patients in early chronic stroke. The timing of CIMT is important, as early application (10 days poststroke) was not more effective than traditional therapy.[9] Overall, there is moderate evidence that CIMT may be effective[10] for poststroke recovery, but specific protocols and timing have yet to be defined for widespread clinical adoption.

Received May 12, 2018; final revision received September 23, 2018; accepted October 4, 2018.

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(*Stroke*. 2018;49:3107-3114. DOI: 10.1161/STROKEAHA.118.021359.)

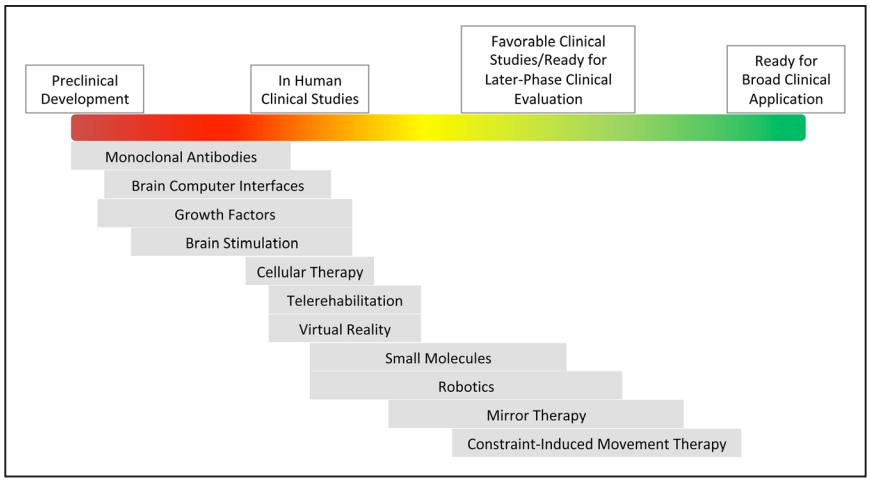

Figure. Summary of current experimental treatments for stroke recovery and their readiness for incorporation into clinical practice based on synthesis of current evidence. Readiness for clinical application ranges from preclinical development (ie, in animal studies only, red) to broad clinical application (green).

Small Molecules

The 2 classes of drugs that have been most investigated as stroke recovery treatments to date are serotonergic and dopaminergic. Building on prior smaller studies, the FLAME study (Fluoxetine for Motor Recovery After Acute Ischemic Stroke) was a double-blind, placebo-controlled trial in which 118 patients with weakness after ischemic stroke were randomized to 3 months of oral fluoxetine or placebo, 5 to 10 days poststroke.[11] Patients with clinical depression were excluded. Those randomized to fluoxetine showed significantly greater motor recovery to 90 days poststroke on the FM Motor Scale than those receiving placebo (a 9.8 point boost in recovery on the 100 point total FM for upper+lower extremities, largely driven by the upper extremity where fluoxetine-related gains exceeded the MCID of 5.25 points in chronic stroke[12]), as well as a significantly less disability as measured by the mRS; interpretation is complicated by mild baseline imbalances favoring the fluoxetine group. A meta-analysis of 52 trials of selective serotonin reuptake inhibitors (SSRIs) after stroke found that at the end of treatment, patients receiving an SSRI were less likely to be dependent, disabled, neurologically impaired, depressed, or anxious and that favorable effects were greater in participants who were depressed at randomization.[13] Phase III trials examining SSRIs for stroke recovery are ongoing. Several mechanisms might account for the potential efficacy of SSRIs for stroke recovery, including reducing neural inflammation, enhancing neurotropic effects, and modulating excitatory/inhibitory synaptic and cortical network balance.[14,15]

Given their well-established role in reward, learning, and neural plasticity, dopaminergic drugs have also been investigated for poststroke recovery. In 2001, a single-center (inpatient rehabilitation facility), randomized, placebo-controlled study of 53 patients with ischemic stroke that occurred 3 weeks to 6 months previously showed that a dopaminergic drug (Sinemet 100 mg/d) improved motor recovery measured using the Rivermead Motor Assessment.[16] More recently, the Dopamine Augmented Rehabilitation in Stroke trial was a multicenter, randomized, double-blinded, placebo-controlled trial with some pragmatic design features that examined 6 weeks of Sinemet 100 mg/d given before rehabilitation therapy in 593 patients recruited 5 to 42 days poststroke and found no difference between groups in the primary end point, walking independently.[17] Overall, stroke recovery studies with dopaminergic drugs have been mixed, likely reflecting complex interactions between learning, reward, environment, psychology, cognition, and genetics.[18] Stroke recovery is not a one-size-fits-all science, and so these results suggest the need to identify the optimal target population and conditions for therapies targeting dopaminergic neurotransmission.

Other small molecules, including noradrenergic[19] and cholinergic[20] drugs, have recently been explored for poststroke recovery. Amphetamines have been extensively studied, with

Table. Main Points

Stroke recovery trials target a different biology with a different time course as compared to acute stroke trials.
Stroke recovery trials target brain tissue, not vasculature.
Acute phase treatments (reperfusion, neuroprotection) have a time window measured in minutes and hours, whereas recovery treatments have time windows measured in days, week, months, or years.
Recovery treatments are not targeted to rescue dying brain tissue but rather to promote neural repair in remaining tissue.
Many new promising strategies are on the horizon for stroke recovery.
Trials of treatments targeting stroke recovery benefit from employing modality-specific end points to obtain the granularity needed to measure differences in recovery across different neural systems (eg, recovery of language vs gait).
The time window for many recovery trials affords the opportunity to measure behavior at baseline and thus change in behavior, which in turn enables within-subject assessment of recovery.
The choice of the study population for recovery studies can strongly influence how well preclinical results are accurately translated and how well study hypotheses are truly tested.

mixed results, and a meta-analysis suggested that too few patients have been studied to draw conclusions.[21] Building upon favorable preclinical studies,[22] a phase IIa trial in France and Spain (https://www.clinicaltrials.gov; unique identifier: NCT02928393) of Basmisanil, a gamma-aminobutyric acid negative allosteric modulatory drug, was initiated but was terminated prematurely after 9 months (enrollment was slow—only 5 patients had been enrolled towards the goal of 95). A key insight from preclinical studies of neurotransmitter strategies is that a drug that improves recovery when initiated days after stroke onset can cause poorer outcomes if initiated too early,[22,23] reaffirming a longstanding observation in stroke recovery pharmacology that recovery drugs often have biphasic effects depending on time of initiation poststroke.

Few traditional and alternative medicines have been studied using formal research methods. One exception is the CHIMES study (Chinese Medicine Neuroaid Efficacy on Stroke Recovery),[24] a multicenter, double-blind, placebo-controlled clinical trial that randomized 1100 patients to 3 months of Neuroaid versus placebo, provided in the form of 3 daily doses of 4 oral capsules each. Neuroaid is a traditional Chinese medicine containing extracts of 9 herbal and 5 animal components. Patients started therapy within 72 hours of stroke onset. No difference between treatment arms was seen in the primary outcome measure, shift in the mRS at 3 months.

In summary, some small molecules are ready for late-phase trials and indeed are underway, whereas others are in earlier stages of development or require study with respect to specific patient subgroups or conditions. Timing of drug initiation is critical and can be informed by preclinical studies, as well as time window-finding studies in humans. Personalized medicine approaches can likely maximize benefit from small molecules for promoting stroke recovery, for example, enrolling subjects with attention to key genetic factors or pairing drug exposure with optimized reward or training. Combining small molecules with appropriate repetitive neurorehabilitation training may also be promising.

Growth Factors

After stroke, many growth factors show increased levels for several weeks, playing a critical role in spontaneous neural repair through mechanisms that include neural sprouting and new synapse formation, angiogenesis, reduced apoptosis, stem cell proliferation, and immunomodulation.[25] One strategy to promote stroke recovery, therefore, is to increase levels of key growth factors.[26] Numerous preclinical stroke studies suggest that administration of exogenous growth factors ≥24 hours poststroke significantly improves outcome, for example, using fibroblast growth factor,[27] brain-derived neurotrophic factor,[28] epidermal growth factor plus erythropoietin,[29] or beta-human chorionic gonadotropin (b-hCG) followed by erythropoietin.[30]

Systemic erythropoietin enters the brain and when introduced with a delay after stroke (eg, ≈24 hours) can improve outcomes.[31] Favorable effects of this growth factor have been described in other preclinical studies that used sequential administration of epidermal growth factor[29] or b-hCG[30] followed by erythropoietin, beginning 1 to 7 days after stroke. This approach was studied in the BETAS study (B-hCG+Erythropoietin in Acute Stroke), a single-dose, open-label, noncontrolled safety trial of b-hCG (initiated 1–2 days poststroke) followed by intravenous erythropoietin (initiated 7–8 days poststroke), which successfully demonstrated safety.[32] The REGENESIS Study (Study of NTx™-265: Human Chorionic Gonadotropin [hCG] and Epoetin Alfa [EPO] in Acute Ischemic Stroke Patients)[33] was intended to be a randomized, placebo-controlled, double-blind proof of concept study of sequential b-hCG and erythropoietin using the BETAS study treatment schedule. This trial was put on hold because of concerns arising from a previous acute neuroprotection stroke trial[34] that initiated erythropoietin <6 hours after stroke onset and found increased drug-related mortality rates, despite the fact that the REGENESIS trial targeted a different time window and biology (erythropoietin initiated <6 hours after stroke in the acute trial versus REGENESIS trial which waited until 7–8 days poststroke). As a result, the REGENESIS trial was modified to be a dose-ranging safety study, and treatment groups did not differ in NIHSS score change at day 90. Growth factors are likely appropriate for further clinical study—development would benefit from clearer direction from preclinical studies for insights into mechanism of action (informing target human population), dosing, and optimal timing.

Monoclonal Antibodies

In the central nervous system, 3 inhibitors (MAG [myelin-associated glycoprotein], oligo-myelin glycoprotein, and neurite outgrowth inhibitor-A) increase levels poststroke and result in lack of a permissive growth environment.[35] Monoclonal antibodies can neutralize these inhibitors by modulating activity in targeted signaling pathways, thus promoting axonal growth and potential recovery. One study[36] randomized 42 patients with stroke to 2 rounds (24–72 hours poststroke and 9 days later) of placebo versus 1 of 3 dose levels of intravenous GSK249320, a humanized IgG1 monoclonal antibody to MAG with disabled Fc region. No safety concerns were identified, and results suggested that the antibody improved gait recovery. A subsequent phase II study[37] compared the highest intravenous GSK249320 dose level to placebo in 134 patients with stroke 24 to 72 hours prior. Although administration of the antibody resulted in lower free serum MAG levels, the primary end point, change in gait velocity from baseline to day 90, did not differ between groups. Effective antibody activity was confirmed in the periphery but was not assessed in the central nervous system. In summary, monoclonal antibodies would benefit from further preclinical development followed by further early phase clinical study.

Cellular Therapy

Cell treatments have multiple effects in the poststroke brain. Transplanted cells might integrate into the existing brain architecture replacing cells lost to stroke; secrete cytokines, growth factors, and extracellular matrix proteins; or modify systemic immune responses to stroke aiding functional recovery. In a randomized, double-blind, placebo-controlled Phase 2 study, Hess et al[38] delivered allogeneic marrow-derived cells intravenously to 126 patients early (24–48 hours) after ischemic stroke. Cell administration was safe, but no significant efficacy signal was seen in the primary end point: excellent outcome at

day 90 (mRS score 0–1, NIHSS score 0–1, and Barthel score ≥95). Post hoc analysis at 1-year found a difference in excellent outcome (23% cell-treated versus 8% placebo; *P*=0.02).

In a Phase 1/2 study, Kalladka et al[39] stereotaxically implanted allogeneic immortalized human fetal neurons into the ipsilesional putamen adjacent to focal infarcts in 11 men with stable neurological deficits 6 to 60 months after ischemic stroke. There were 3 serious adverse events during the first month postprocedure: 2 asymptomatic intracranial hematomas attributed to the procedure and 1 symptomatic infarct attributed to preprocedure suspension of antiplatelet drugs. Nonserious adverse events were mostly mild. Several patients showed treatment-related improvement, including on NIHSS, Ashworth scale, and Barthel Index.

In a single-arm, open-label study, Steinberg et al[40] stereotaxically implanted allogeneic modified marrow-derived mesenchymal cells into tissue surrounding focal infarcts in 18 patients with stable deficits 6 to 60 months after ischemic stroke. Cell implantation appeared safe, with reversible adverse events largely related to the surgical procedure. During 1-year follow-up, significant improvements were seen in the European Stroke Scale, NIHSS, and FM scores, with no significant changes in mRS.

In summary, early studies suggest that systemic and intracranial cell administration is feasible and may prove safe and effective as treatments for promoting neurological recovery early and late after stroke. Optimal dose, route, and timing of cell administration remain underexplored. Further randomized, double-blind, placebo-controlled trials are needed and are ongoing.

Brain Stimulation

Several forms of brain stimulation have been investigated to enhance recovery after stroke, most in small studies. Some aim to increase activity, for example, with high-frequency repetitive transcranial magnetic stimulation,[41] whereas others aim to reduce activity in areas thought to have an undesired suppressive effect, for example, with low-frequency repetitive transcranial magnetic stimulation.[42] Similar approaches have been advanced for transcranial direct current stimulation,[43] where electrodes broadly apply current through the scalp in the treatment of several different types of poststroke deficits including motor, language, memory, and neglect. An advantage of transcranial direct current stimulation is it is readily applied during rehabilitation. Meta-analyses have concluded that more evidence is needed to establish benefit.[44,45] Two recent studies showing positive effects of transcranial direct current stimulation after stroke raise enthusiasm, one targeting dysphagia during the acute stroke hospitalization[46] and the other targeting chronic aphasia.[47] These highlight issues of capitalizing on anatomic substrates of neurological function (eg, bihemispheric control, for swallowing; unilateral dominant hemisphere control, for language), as well as importance of considering timing of intervention poststroke.

Other approaches for brain stimulation are under study, including deep brain stimulation. A phase III trial did not find a significant benefit from epidural cortical stimulation combined with rehabilitation compared with rehabilitation alone in patients with chronic stroke.[48] Vagus nerve stimulation has been hypothesized to enhance brain plasticity, possibly by modulating activity in neurotransmitter systems, such as acetylcholine and norepinephrine.[49] A recent randomized human clinical trial of vagal nerve stimulation paired with rehabilitation demonstrated safety and feasibility,[50] and efficacy trials are ongoing.

To advance brain and nervous system stimulation for the treatment of stroke recovery, further clinical and possibly preclinical studies (preclinical studies have been limited to date) are needed to inform mechanism, dose, intensity, and optimal targets to maximize effects.

Robotics

Robots are promising for stroke rehabilitation because they can deliver consistent, programmable, and high-intensity motor therapy, and furthermore can use sensors to measure movement kinematics. Numerous robotic systems have been studied.[51] A 2010 multicenter study of 127 patients conducted within the Veterans Health Administration system showed that robot-assisted therapy did not significantly improve motor status at 12 weeks, the primary end point, as compared with usual care or intensive therapy. A delayed favorable effect as compared with usual care, however, was suggested in secondary analyses for 36 weeks.[52] This study may have been limited by its choice of study population, enrolling patients with severe deficits in the chronic phase poststroke, among whom producing substantial benefits is challenging. Numerous other studies spanning different recovery stages for the past 20 years have demonstrated economic feasibility[53] and therapeutic benefits of robot therapy. Benefits of robot-assisted therapy for the upper extremity, however, are attributable to the intensity and repetition of movement practice,[54] and robot-mediated therapy has not demonstrated clear additional benefits when compared with physical therapy when intensity and number of movement repetitions have been matched.[55] Moreover, a recent Cochrane review of robot-assisted and electromechanical arm training devices for improving arm function after stroke found only low-quality evidence that such interventions improve activities of daily living.[56]

For the lower extremity, meta-analyses have shown that adding electromechanical-assistance (robot-assistance) to body weight support increases the odds of patients becoming independent with walking.[57] However, a large clinical trial did not find body weight supported treadmill training to be superior to progressive exercise at home managed by a physical therapist in patients 2-months poststroke.[58] American Heart Association/American Stroke Association Guidelines describe Class IIb evidence supporting mechanically assisted walking with body weight support for patients who are nonambulatory after stroke.[59]

Overall, Phase 2 and possibly Phase 3 studies of robotics for stroke recovery are needed that enroll populations most likely to benefit or that test engineering approaches targeting improved functional outcomes using methods that build on the unique strengths of robots. Further development of robotic interventions might also include adjusting robot movements to patterns of disrupted movements and linking robot assistance to cortical activity (ie, brain-computer interfaces [BCI]).

Brain-Computer Interfaces

When a lesion is severe, one potential approach to restoring voluntary behavior is to capture signals from intact cortex and bypass the lesion. Some advocate a surgical approach. A recent study in patients with spastic arm paresis due to various diagnoses (25% were because of stroke), an average of 15 years after the event showed that C7 nerve transfer from the nonparalyzed to paralyzed body side was associated with a 15 point increase in the FM arm score in the affected arm, exceeding the MCID for the upper extremity of 5.25 points in chronic stroke[12] and with sustained improvements as compared to controls (rehabilitation alone) at 1 year.[60]

An alternative approach to lesion bypass is a BCI. A BCI is a system that may or may not be noninvasive and that translates central nervous system signals into command signals for a technological device. The components of a BCI include devices for recording neural signals (sensors), the process of translating neural signals into command signals (neural decoding), devices for executing command signals (effectors), and the feedback provided to the user (feedback). Using BCI systems, people with neurological disease have successfully controlled computer cursors to regain communication and robotic prosthetics to restore movement.[61] A complementary goal of BCI is to enhance rehabilitation therapy effects.[62] The hypothesis is that training patients to produce normal brain activity patterns through feedback reinforcement or linking neural activity directly to sensory feedback of intended actions engages activity-dependent Hebbian neuroplasticity mechanisms and thereby restores native neurological functions. Initial studies in patients with chronic stroke have been promising, for example, electroencephalography-BCI training with an upper extremity orthosis produced a 3.4-point significant positive difference in the FM arm motor score compared with controls. Although shy of the MCID, behavioral gains in the experimental group correlated with adaptive changes in functional magnetic resonance imaging neural activity pattern, arguing that BCIs may induce clinically useful neuroplastic changes.[63] Another recent study[64] showed that use of an electroencephalography-driven exoskeleton to open and close the affected hand using signals from the contralesional (unaffected) hemisphere significantly improved arm function (6.2 point increase on the Action Research Arm Test score, exceeding the 5.7 point MCID[65] in chronic stroke). This study was notable given the use of signals from the unaffected hemisphere and delivery of therapy at home. Advances in BCI will benefit from a deeper understanding of how to facilitate personalized neural signals to enhance neuroplasticity, as well as a more nuanced understanding of circuit function in spontaneous recovery after stroke. More generally, the paradigm of closed-loop neurotechnological devices, in which sensing neural activity is coupled with effecting change in the nervous system, is a promising neurorehabilitation approach. Further preclinical study and early phase clinical development are needed.

Telerehabilitation

Task-based practice improves outcomes after stroke in a dose-dependent manner and also provides the behavioral component of the experience-dependent plasticity that is facilitated by many restorative therapies. However, patients often do not receive large doses of supervised practice because of issues such as cost, difficulty traveling to appointments, and regional provider shortages. Telehealth might provide new means to achieve high doses of therapy in an accessible manner using communication technologies. One recent study evaluated a home-based telerehabilitation system in patients with chronic hemiparetic stroke with onset 3 to 24 months prior.[66] Enrollees received 28-days of telerehabilitation prescribed and supervised by licensed therapists using a system delivered to the patient's home, each day consisting of 1 structured hour focused on individualized exercises and games, stroke education, plus an hour of free play. Compliance was excellent: participants engaged in therapy on 97.9% of assigned days, a substantial improvement over traditional home exercise programs. Arm repetitions averaged 879 per day, far exceeding the 32 repetitions found with standard of care therapy[67] and approximating the several hundred movements per day found in primate studies as important to achieving optimal post-stroke motor cortex plasticity.[68] Arm motor status showed significant gains, with half of the participants exceeding the arm motor FM score MCID. This approach did not require computer skills, levels of which were unrelated to motor gains or system use. A multisite phase II trial is now underway (https://www.clinicaltrials.gov; unique identifier: NCT02360488). Meta-analyses of telerehabilitation after stroke have found either better or similar effects when compared with conventional in-person therapy but have noted high heterogeneity in treatment content across studies.[69,70] Further clinical development of telerehabilitation to optimize dose and standardize protocols is warranted before late-phase clinical trials.

Virtual Reality and Movement Sensors

There is converging evidence that high-dose, repetitive, task-oriented, and task-specific training is beneficial, at least for selected patients after stroke.[71,72] The key is not simply a greater number of repetitions but also task salience and specific attention to time poststroke and external environment.[73–76] Virtual reality (VR), ranging from nonimmersive to fully-immersive depending on the degree to which the user is isolated from his or her physical surroundings when interacting virtually, has been used as an alternative and as an adjunct to conventional rehabilitation. VR provides a scalable means to deliver high-intensity, task-specific training, as well as real-time feedback (ie, rewards for positive trials) potentially with enhanced salience. However, the evidence for efficacy of VR to date has been mixed.[77–80] Well-designed studies that build on prior work are needed, possibly maximizing salience to individual patient factors.

Movement sensors are another means of providing feedback with the goal of motivating greater skills practice and thus improving rehabilitation. In this regard, lower extremity sensors providing simple measures of physical activity and gait are more developed than upper extremity sensors, for which accurately characterizing reaching and grasping movements represents an ongoing computational challenge.[81] In one lower extremity sensor feasibility study, participants were given feedback of walking metrics via ankle sensors. This augmented feedback did not increase time spent practicing or improve walking outcomes in a rehabilitation setting as compared to

therapists providing feedback on walking speed alone (without the use of ankle sensors).[82] A recent review found some evidence that lower extremity wearable sensors improved outcomes, but the design of studies included was highly variable.[83] As with VR, additional earlier phase studies are needed, particularly those building on principles of personalized intervention.

Summary and Future Directions

This review highlighted contemporary treatment approaches aimed at improving recovery after stroke. Development of stroke recovery treatments will depend on increased understanding of the complex events underlying recovery and development of methods to measure treatment effects in human patients. A key issue is optimal treatment timing, as specific critical periods for most interventions have not yet been defined. Trial design is also paramount, for example, end points targeting a single domain (motor, language, etc) may be more informative than global outcome measures that combine data from multiple different domains. Outcome measures benefit from having sufficient granularity to detect useful functional gains and being informative about the biology of recovery—global outcome measures, such as the mRS, may have critical shortcomings in this regard. As the efficacy and mechanism of individual treatments targeting stroke recovery are better understood, combinations of existing and novel therapies will warrant investigation.

Stroke recovery trials offer the opportunity for rigorous testing, for example, at baseline as entry criteria or stratification variables. Serum, genetic, imaging, and neurophysiologic data may be useful as predictors.[84] For example, motor response to transcranial magnetic stimulation[85] differentiates patients likely to experience spontaneous motor recovery from those who will not. An imaging-based measure of corticospinal tract injury can prospectively identify responders to rehabilitation therapy in chronic stroke.[86] Some of these measures can be serially collected as biomarkers of treatment effect.

The field of stroke recovery continues to benefit from the combination of perspectives of clinicians caring for stroke patients, as well as the scientists elucidating biological mechanisms of recovery and developing new recovery-promoting technologies. These groups bring invaluable insights.

Sources of Funding

This work was supported by grants from the National Institutes of Health (R25NS065743, R44NS095381, and K24HD074722).

Disclosures

Dr Lin has consulted for Boehringer Ingelheim; Dr Cramer, for MicroTransponder, Roche, Dart Neuroscience, Neurolutions, Regenera, Abbvie, SanBio, Constant Pharmaceuticals, and TRCare; and Dr Finklestein, for Constant Pharmaceuticals and AZTherapies, and he is a Principal in Stemetix.

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KEY WORDS: brain ■ clinical trials ■ rehabilitation ■ stroke ■ therapeutics