HHS Public Access

Author manuscript

Curr Atheroscler Rep. Author manuscript; available in PMC 2018 February 07.

Published in final edited form as:

Curr Atheroscler Rep. ; 19(12): 59. doi:10.1007/s11883-017-0686-6.

Early Rehabilitation After Stroke: a Narrative Review

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Abstract

Purpose of Review—Despite current rehabilitative strategies, stroke remains a leading cause of disability in the USA. There is a window of enhanced neuroplasticity early after stroke, during which the brain's dynamic response to injury is heightened and rehabilitation might be particularly effective. This review summarizes the evidence of the existence of this plastic window, and the evidence regarding safety and efficacy of early rehabilitative strategies for several stroke domain-specific deficits.

Recent Findings—Overall, trials of rehabilitation in the first 2 weeks after stroke are scarce. In the realm of very early mobilization, one large and one small trial found potential harm from mobilizing patients within the first 24 h after stroke, and only one small trial found benefit in doing so. For the upper extremity, constraint-induced movement therapy appears to have benefit when started within 2 weeks of stroke. Evidence for non-invasive brain stimulation in the acute period remains scant and inconclusive. For aphasia, the evidence is mixed, but intensive early therapy might be of benefit for patients with severe aphasia. Mirror therapy begun early after stroke shows promise for the alleviation of neglect. Novel approaches to treating dysphagia early after stroke appear promising, but the high rate of spontaneous improvement makes their benefit difficult to gauge.

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This article is part of the Topical Collection on *Cardiovascular Disease and Stroke*

Compliance with Ethical Standards

Conflict of Interest Drs. Coleman, Moudgal, Lang, Hyacinth, Awosika, and Feng have nothing to disclose.
Dr. Kissela was a consultant for Ipsen, received fees for adjudication of clinical trial events for AbbVie and Janssen and grants from the NIH/NINDS.

Human and Animal Rights All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

Summary—The optimal time to begin rehabilitation after a stroke remains unsettled, though the evidence is mounting that for at least some deficits, initiation of rehabilitative strategies within the first 2 weeks of stroke is beneficial. Commencing intensive therapy in the first 24 h may be harmful.

Keywords

Stroke rehabilitation; Early rehabilitation; Stroke recovery; Neuroplasticity; Motor recovery; Aphasia

Introduction

When should rehabilitation commence after a stroke? This seemingly simple question is in fact far from simple and remains unsettled. Evidence from animal studies shows that after ischemic injury, a cascade of genetic, molecular, cellular, and electrophysiological events is triggered which promote neural recovery. Together, these events drive cortical reorganization and regeneration, and provide the neural substrate for spontaneous recovery. In rodent models, these events begin within hours after stroke, peak at 7–14 days, and are nearly complete at 30 days [1]. This time course coincides with the period of maximal spontaneous recovery in rodents, which has been shown in numerous studies to take place almost entirely within the first month after stroke [2–4]. Researchers have long hypothesized that neuroplasticity during the dynamic early period after stroke can be augmented and perhaps prolonged. Results from clinical studies based on this hypothesis, however, have been inconclusive and inconsistent. Moreover, concern has emerged, first in animal models and more recently in human trials, that rehabilitation delivered too early, or too intensively during the very early period (i.e., within the first 24 h after stroke), may be harmful. Herein, we first provide a brief overview of the underlying neuroplastic changes that occur after stroke, including changes in gene expression and regulation, and examine the evidence from animal models for both benefit and harm from early rehabilitation. We then turn our attention to the recent literature on early post-stroke rehabilitation, focusing on clinical trials published within the past 5 years. For the purpose of this review, we have defined “early rehabilitation” as interventions beginning within 2 weeks of acute stroke, and with few exceptions, we will not discuss trials outside of that time frame. Research on rehabilitation in this interval is quite sparse, largely due to logistical challenges, including medical instability in many acute stroke patients, and the difficulty of conducting research across different care settings in the USA. Other authors have noted the marked discrepancy between the period in which most post-stroke rehabilitation is provided (acute-to-subacute), and the period in which most rehabilitation research is conducted (chronic) [5]. This discrepancy leads to a dearth of high-quality evidence on best practices and mechanisms of recovery during the crucial first days after stroke. The goal of this review is to explore existing evidence regarding rehabilitation in the early period after stroke, in the domains of mobility, upper extremity function, language, neglect, and dysphagia.

Neuroplastic Changes Following Stroke

Cortical Reorganization

One of the fundamental elements of post-stroke neuroplasticity is cortical reorganization, a process in which functions of the damaged brain migrate to other, uninjured brain regions. In mice, within 1–3 days of stroke, stimulation of limbs contralateral to the stroke produces activity in the ipsilateral cortex, indicating reorganization of sensory inputs to the intact hemisphere. By 1–2 weeks post-stroke, activity shifts back to the injured hemisphere, with spared perilesional cortex taking on functions of the damaged brain [6–8]. Numerous fMRI and PET studies have demonstrated the same sequence of events in humans, in both motor [9–11] and language domains [12]. While the transient shift of activity to the contralesional hemisphere is probably adaptive, in both human and animals, the degree to which function shifts back to the injured hemisphere correlates with the degree of behavioral recovery [1, 13]. The time course of cortical reorganization is less clear in humans than in animals, though a few fMRI studies suggest that it is similar, with activity beginning to shift back to the injured hemisphere at about 2 weeks post-stroke [13]. However, it is important to note that the period of brisk spontaneous recovery lasts longer in humans than in rodents—at least 3 months as opposed to 1 month—and therefore the period of maximal neuroplasticity in humans is not entirely clear [11, 13, 14].

Structural Change and Regeneration

Neural plasticity and functional recovery after stroke is underpinned by structural changes in the brain. In animal models, ischemia induces sprouting of new dendrites and axons, primarily in the perilesional cortex but also in regions remote from the lesion. Growth-factor signals promoting synaptogenesis can be detected as early as 3 days post-stroke and peak at 7–14 days [15, 16]. Stroke also triggers angiogenesis, which is well established within 10 days of stroke in rats [17] and results in the development of collateral vessels to support the ischemic penumbra. Newly sprouted vessels may also serve as scaffolds to support the migration of neural stem cells from their reservoir in the subventricular zone (SVZ) to the infarct bed [18].

Genetic and Epigenetic Changes

Perhaps the most widely studied single gene in relation to post-stroke outcome is brain derived neurotrophic factor (BDNF). BDNF is a member of the nerve growth factor family of proteins. It has numerous effects relevant to post-stroke recovery, including neurogenesis, neuronal differentiation and survival in response to cerebral ischemic insult, and suppression of apoptosis [19–21]. BDNF has been reported to play a significant role in synaptic plasticity [22] and may be important in post-stroke cognitive recovery. In a rat middle cerebral artery (MCA) occlusion model of stroke, exogenous administration of BDNF resulted in reduced infarct volume and improved sensorimotor function [23–25].

The role of epigenetics in post-stroke recovery has recently come to the fore with exciting findings [26–28]. Recent investigation suggests that microRNA (miRNA) play an important role in the molecular response to cerebral ischemia. miRNA are short non-coding RNA, which regulate gene expression by binding to messenger RNA and silencing it. One newly

discovered miRNA target that may play a role in early and late post-stroke outcome is methyl-CpG-binding protein 2 (MeCP2). MECP2 is a regulator of transcription found abundantly in neurons, involved in neuronal growth and maturation [29]. One study showed that MECP2 knockout mice had significantly larger infarct sizes compared to wild type after an induced stroke [30]. In neurons, interaction of the MECP2 mRNA with miRNA-132 represses MECP2 protein expression.

Overall, more research is needed in this area, as genetic polymorphisms and differential gene regulation could provide both early biomarkers for recovery and targets for rehabilitation therapy.

Evidence for the Benefit of Early Rehabilitation in Animal Models

Numerous studies have shown that animals exposed to locomotor exercise beginning 24–48 h post-stroke have better behavioral outcomes and smaller ischemic volumes than control animals who receive delayed or no exercise training [31–35]. One study directly compared initiation of treadmill training at different time points and found behavioral gains in rats who began training at 5 days, and to a lesser extent 14 days, but not 30 days post-stroke. Histologically, the two early groups showed increased dendritic sprouting, supporting the idea that exercise induces cellular changes, and thereby promotes recovery, *only* during the plastic window [36]. Other groups have found evidence that early exercise (commencing 24–72 h post-stroke) decreases inflammatory cytokines [33, 37], tightens the blood-brain barrier [38], suppresses apoptosis [39, 40], increases BDNF [41], and promotes neurogenesis [40, 42].

Evidence for Harm of Early Rehabilitation in Animals

While the preponderance of animal data favors early exercise, several experiments have suggested that under certain circumstances, therapy very early may be detrimental. Li et al. found that exercise beginning 6–24 h post-stroke led to an increase in inflammatory cytokines, whereas the same exercise commencing 3 days post-stroke decreased those cytokines [43]. Likewise, Risedal et al. found that exercise training in rats beginning at 24 h post-stroke was associated with enlargement of ischemic lesions compared with animals who began training at 7 days, though the early and late training groups performed similarly on behavioral tests [44]. Another study exposed rats to voluntary exercise starting 24 h post-stroke and found that the exercise group had worse functional outcomes and less neuronal proliferation in the SVZ at 1 week [45]. Kozlowski et al. found that immobilizing the unaffected forelimb in rats immediately after stroke resulted in significantly worse behavioral outcomes and retardation of dendritic sprouting, which the authors attributed to early overuse of the affected forelimb [46]. This finding is noteworthy because the immobilization method is analogous to constraint-induced movement therapy (CIMT), so the negative result generated concerns about initiating CIMT very early after stroke. It is important to note that two of these four studies began therapy at < 24 h, supporting the idea that the first 24 h post-stroke may be a vulnerable period, and a third study found “harm” on a tissue but not on a behavioral level. While there are a few outliers, the majority of animal studies show benefit of exercise therapy once the first 24 h have elapsed.

Human Trials

Very Early Mobilization

Recently, a hypothesis has gained currency that the traditional practice of forced bedrest after stroke may be harmful, and that mobilizing patients as early as possible might prevent complications and promote recovery in humans. In the past 5 years, four trials have sought to test this hypothesis. The largest and most robust is the multicenter AVERT (A Very Early Rehabilitation Trial for Stroke) [47]. AVERT tested a very early mobilization (VEM) protocol consisting of three core elements: (1) initiation within 24 h of stroke onset; (2) focus on out-of-bed (OOB) activity (i.e., sitting, standing, and walking); and (3) addition of at least three OOB sessions to standard care (SC). To the researchers' surprise, AVERT found a small but significant *reduction* in the odds of a favorable outcome (modified Rankin Scale [mRS] 0–2) at 3 months after stroke in the VEM group. One notable limitation of this trial is the shift in practice to earlier onset of therapy within the SC group over the course of the trial, with roughly 60% of SC patients starting out of bed therapy within 24 h of stroke onset. As a result, the difference between the intervention and control groups regarding time to first mobilization, though statistically significant, was small—mean 18.5 versus 22.4 h. The difference in intensity, however, was large, with the intervention group spending almost three times longer OOB than controls (mean 201.5 versus 70 min), and this probably had a greater impact on outcomes than the difference in time to first mobilization. Though not statistically significant, the complication with the largest between-group difference was stroke progression. Thus, the AVERT trial may provide preliminary evidence for a relationship in humans between intensive, very early activity and infarct expansion. Designed as a pragmatic trial, AVERT also suffered from lack of standardization of the therapy intervention, particularly in the SC group. Additional limitations include the bluntness of the mRS as an outcome measure, especially for a recovery trial in which the potential benefit of the intervention is likely to be subtle, and the lack of information on stroke subtype. There is a plausible biological argument, albeit unproven, that individuals with large vessel disease are especially vulnerable to deterioration from prolonged upright positioning. Therefore, analyzing treatment response by subtype, and perhaps even stratifying by subtype in the randomization, might have identified populations more or less likely to benefit from (or be harmed by) the intervention.

To further delineate practical clinical guidance with respect to optimal timing, frequency, and quantity of OOB activity, the AVERT group completed a pre-specified dose-response analysis of all trial participants, irrespective of group assignment [48]. They examined three characteristics of dose: (1) time from stroke onset to first mobilization, (2) median number of OOB sessions per day, and (3) median minutes of OOB activity per day. This analysis suggested that shorter and more frequent early mobilization—not exceeding 10 min per session, in at least 2 and as many as > 10 sessions per day as tolerated, with no upper limit on the number of sessions—can improve the chances of regaining independence after stroke, controlling for age and severity. Specifically, it showed 13% increased odds of a favorable outcome with each additional OOB session per day, keeping the time to first mobilization and daily amount constant. Conversely, increasing the amount of time spent in OOB activity,

while keeping the frequency and time to first mobilization constant, reduced the odds of a favorable outcome.

In a 2012 trial, Sundeth et al. randomized stroke patients who presented within 24 h of stroke onset to very early mobilization (VEM) within 24 h of admission or mobilization between 24 and 48 h admission. Subjects in the VEM group were mobilized at mean 13 h from stroke onset, compared with mean 30 h in the delayed group [49]. Results showed a non-significant trend toward poorer outcome (mRS 3–6) and higher rates of death and dependency among patients in the VEM group. This small trial ($n = 56$) was underpowered and therefore inconclusive, but in light of the AVERT trial, it adds to the concern that mobilization within 24 h might be detrimental. Another multicenter RCT, AMOBES (Active Mobility Very Early After Stroke) [50], compared 20 min per day of “soft” physical therapy (PT) (passive range-of-motion exercises aimed at preventing immobility-related complications) with soft PT plus 45 min of active intensive exercises, both commencing within 72 h of stroke. This trial found no difference in motor impairment at 90 days, as measured by the Fugl-Meyer Motor Scale (FMMS). Limitations of this trial include relatively low sample size ($n = 104$), frequent protocol deviations, and a study population that differed in certain aspects from the typical stroke population. For example, the relatively young study subjects had higher rates of severe stroke, very low motor control, but a relatively low death rate.

Only one prospective mobilization trial was positive. Chippala et al. [51] used a VEM protocol modeled after AVERT’s, with 5–30-min sessions of OOB activity at least twice a day for 7 days, beginning within 24 h of stroke onset, in addition to SC (defined as 45 min a day of passive and/or active exercises, with mobilization occurring at the therapists’ discretion). The primary outcome was change in functional status (Barthel Index [BI]) from baseline to hospital discharge. The intervention group was mobilized on average 12 h earlier (18 versus 30 h post-stroke), and had significantly greater improvement in BI than controls (median 35 versus 17.50, $p < 0.001$). This difference was partially sustained at 3 months. While the findings of this trial should not be ignored, they must be viewed in context of significant limitations, namely small sample size ($n = 86$) and the possibility of confounding factors after a short 7-day intervention.

One recent observational study is worthy of mention. Momosaki et al. sought to clarify the association between early rehabilitation, defined as any physical or occupational therapy delivered within 72 h of stroke, and outcomes in acute ischemic stroke patients who received tissue plasminogen activator (tPA) [52]. The primary outcome was functional independence (mRS 0–2) at discharge. Secondary safety outcomes were 7-, 30-, and 90-day mortality, and intracranial hemorrhage. Regression models showed that early rehabilitation was significantly associated with functional independence, with or without adjustment for confounding factors, and there were no significant differences in any safety outcomes. While this study had pitfalls typical of retrospective studies, including limited data on the intensity and nature of therapy delivered, it provides reassurance on the safety of mobilizing stroke patients early after tPA and suggests that doing so may be beneficial. It should be noted that the 72-h time frame differs from AVERT and the other early recovery trials.

Physiotherapeutic Approaches: Lower Extremity Function and Gait

We found two good-quality trials of early lower extremity and gait rehabilitation published in the last 5 years. One study investigated the efficacy of Weight Supported Balance Therapy (WSBT) in acute stroke patients, with therapy initiated on average 13 days post-stroke [53]. Patients were randomized to WSBT plus standard PT or standard PT alone, and the primary outcomes were pre-post-intervention changes in Fugl-Meyer Balance (FM-B), Functional Independence Measure Gait (FIM-G), and Fugl-Meyer Lower Extremity (FM-LE). No significant differences were seen between the two groups on any of the outcome measures.

A recent multicenter study examined the role of timing for two different commonly used physical therapy programs: Proprioceptive Neuromuscular Facilitation (PNF) and Cognitive Therapeutic Exercise (CTE) [54]. In this study, 340 subjects, all of whom presented within 24 h of stroke onset, were randomized to one of the four treatment groups: early PNF, delayed PNF, early CTE, or delayed CTE. The early groups began therapy within 24 h of admission (i.e., within 48 h of onset); the delayed groups began 4 days after stroke onset. All groups received 60 min of therapy, which was a mix of in-bed and OOB activity. Primary outcome measures were mRS and BI. No significant differences were observed between groups at 3 months. At 12 months, there was a difference favoring the early groups in BI only, (early PNF and CTE 89 ± 2 and 86 ± 7, respectively; delayed PNF and CTE 71 ± 9 and 73 ± 5, respectively; $p = 0.02$), with no difference seen between the two programs. This study thus shows a benefit of early over later initiation of therapy, but not a robust one, as benefit was seen on only one of the two outcome measures, at only at the 12-month time point. Importantly, most subjects in this study began therapy > 24 (but < 48) hours from stroke onset. Additionally, the quantity of OOB activity, arguably a proxy for intensity of activity, was not recorded in this study, so differences in both the time to first mobilization and the amount of OOB time might be factors in the divergence of these results from those of AVERT.

Upper Extremity

We found three recent trials of early upper limb rehabilitation. The multicenter EXPLICIT-Stroke trials recruited a total of 159 subjects, an average of 8 days after ischemic stroke, and tested two different interventions [55]. For patients with favorable prognoses, defined as ≥ 10° of voluntary finger extension, mCIMT daily for 3 weeks was compared with SC. In the larger second trial of patients without voluntary finger extension ($n = 101$), electromyography-triggered neuromuscular stimulation (EMG-NMS) of the finger extensors was compared with SC. Both EXPLICIT trials used the Action Research Arm Test (ARAT) at 5 weeks from stroke as the primary outcome measure, with additional measures at 8, 12, and 26 weeks. The mCIMT arm of the trial was positive, with a clinically meaningful 6-point difference in ARAT in favor of the treatment group at 5 weeks post-stroke. A statistically significant difference sustained through week 12, but at 26 weeks the difference was no longer significant, due to late improvement seen in the control group. The EMG-NMS trial found no benefit of the intervention over standard care.

A smaller trial ($n = 29$) by Yu et al. also compared mCIMT beginning within 2 weeks of stroke to standard care [56]. The primary outcome measures were Wolf Motor Function Test

score and Motor Activity Log interviews. Although there was an effect seen in favor of mCIMT post-intervention, it was not sustained at 3 months.

A third trial investigated the effect of intensive motor retraining of the upper extremity on neural plasticity [57]. Researchers compared intensive, task-specific upper limb training, which was an extra 30 h of therapy over 3 weeks, against SC, both beginning within 1 week of ischemic stroke. The primary outcome of this study was change in task-related brain activation measured by fMRI at 3 months, and the secondary outcome was improvement in upper limb Motor Assessment Scale. Although the trial was positive, with increased activation seen in the ipsilesional anterior cingulate and supplementary motor areas in the intervention group, there was no difference in functional improvement between the groups at 3 months. Thus, while this study yields interesting information on neuroplasticity, it does not provide evidence to support a clinical benefit of increased intensity in early stroke rehabilitation of upper limbs. When considering intensity, it should be noted that an earlier study (VECTORS) in 2009 found that in patients less than 14 days post-stroke, 3 h per day of CIMT, compared with 1–2 h per day, resulted in *worse* motor outcomes as measured by the ARAT [58]. In contrast to the EXPLICIT trial, VECTORS found that lower dose CIMT was equivalent but not superior to standard therapy; however, the small sample may have precluded statistically significant findings (as it was a pilot trial, no power calculation was performed).

Taken together, these three trials provide convincing preliminary evidence that CIMT in the early phase of stroke recovery may be beneficial. A larger, multicenter trial is warranted to confirm this benefit.

Non-invasive Brain Stimulation in Motor Rehabilitation

Non-invasive brain stimulation (NIBS), which encompasses repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS), has shown increasing promise in modulating the brain activity and improving motor function after stroke. We found four studies investigating NIBS in early stroke motor rehabilitation published in the past 5 years, with excellent safety outcomes but variable efficacy. A 2013 trial by Rossi et al. recruited 50 patients 2 days after ischemic stroke onset and compared anodal tDCS of the lesioned hemisphere against sham stimulation [59]. The primary outcome was FMMS at 5 days and 3 months after stroke. No significant difference was seen between the two groups. A limitation of the study, which may have contributed to the negative results, was inclusion of a wide range of stroke severity and large cortical lesions. tDCS is unlikely be effective if there is no neural substrate to be stimulated (i.e., if primary motor cortex is destroyed) [60].

Another small study enrolled subjects within 7 days of ischemic stroke, and also saw no effect of tDCS by clinical measures [61]. This group performed two separate experiments, the first comparing bilateral tDCS to sham tDCS, and the second pairing tDCS or sham with CIMT. In both experiments, the intervention and control groups performed similarly on behavioral measures. However, the authors reported neurophysiological differences between the groups, measured by transcranial magnetic stimulation (TMS) motor evoked potentials, suggesting that the intervention affected cortical excitability, but not sufficiently to induce behavioral changes.

A 2015 trial by Sattler et al. recruited 20 mild-to-moderately impaired patients at mean 5.5 days after ischemic stroke, and compared ipsilesional anodal tDCS versus sham tDCS, each paired with radial repetitive peripheral nerve stimulation (rPNS) [62]. The primary outcome measure was Jepsen Taylor Hand Function Test (JHFT), and secondary outcome was cortical excitability measured via TMS. The authors observed that most patients regained wrist and finger extension function, but also found an effect in favor of the intervention, with a larger average gain of motor performance in the experimental group in comparison to the sham group. One can speculate that the pairing of tDCS with rPNS was why this study found success where the others did not, but patient selection could also be a critical factor.

Lastly, a 2016 study by Li et al. recruited 12 patients within 5 days of subcortical ischemic stroke and compared repetitive TMS (rTMS) against sham rTMS [63]. Although the primary outcome measure of change in functional connectivity as measured via fMRI found a significant difference between the groups, no effect was seen on the clinically relevant secondary outcome measures.

Most of these NIBS studies are single-centerbased without adequate sample size; therefore, results are mixed and inconsistent. There has been only one multicenter study of tDCS for stroke recovery, published in 2011, which enrolled 96 subjects in the subacute phase (3–8 weeks after stroke). This study compared anodal, cathodal, and sham tDCS stimulation, along with a robotic-assisted device, and did not find a benefit of tDCS [60]. A recent meta-analysis showed that tDCS is more likely to be successful in the chronic phase than in the subacute phase after stroke, though none of the included trials examined patients within 2 weeks of stroke [64]. Additionally, questions remain regarding the optimal dosage/current of tDCS, with a recent study suggesting that doses presently used are far below the safety threshold in animal models [65]. Underdosing could be a major barrier to success in NIBS stroke studies.

Robotics

We identified three studies of robotic interventions in early stroke rehabilitation. A 2013 study tested robotic tilt-table stepper training, beginning within 5 days of ischemic stroke, with or without functional electrical stimulation, against SC [66]. The primary outcome measure was change in Medical Research Council (MRC) strength scale. The study found that leg strength increased significantly in both experimental groups compared to the control group. In 2014, Forrester et al. began rehabilitation of 34 ischemic or hemorrhagic stroke patients within 2 weeks of onset and compared performance-based anklebot training of dorsiflexion and plantarflexion via a racing video game against passive manual stretching [67]. The authors did not find a significant difference between the groups in the primary outcome of walking speed, but reported that the anklebot group had greater measures of symmetry and longer non-paretic step lengths. Finally, Cruz et al. evaluated the efficacy and safety of a tool called SWORD (Stroke Wearable Operative Rehabilitation Device), which combines 3D motion analysis with targeted vibratory feedback, on upper-limb task performance in non-plegic patients with upper limb motor deficit after MCA stroke [68]. Average time from stroke onset to enrollment was 6.8 days, and the primary outcome was the number of correct movements per minute on a hand-to-mouth task. The study found that

vibratory feedback modulated motor training, increasing the number of correct movements by an average of 7.2/min ($p < 0.001$). Taken together, these three small trials show promise in the use of robotics in early stroke rehabilitation.

Aphasia

Early aphasia therapy has been studied in five recent RCTs. The largest and most robust of these is the Rotterdam Aphasia Therapy Study-3(RATS-3) [69], which enrolled 152 subjects in 14 centers across the Netherlands. RATS-3 enrolled patients within 14 days of a first stroke causing aphasia, randomized them to intensive speech therapy (ST), 1 h/day, 5 days/week for 4 weeks, or no therapy, and used the Amsterdam-Nijmegen Everyday Language Test (ANELT) at 4 weeks as the primary outcome. The trial found no benefit of the intervention in the primary, intention-to-treat analysis. Of note, while the intervention group received on average 24.5 h of therapy during the treatment period, a dose considerably higher than typical standard care, only 29% reached the pre-specified minimum threshold of 28 h. In a post hoc, on-treatment analysis, a significant treatment effect was seen in those participants who met the 28 h threshold. This finding must be interpreted with caution, but suggests that intensity may be key to success in early aphasia rehabilitation. At the same time, the trial highlights the difficulty of delivering intense interventions in the very early post-stroke period, when patients' stamina is limited, and there are multiple competing demands on their time (a major reason for failing to reach the 28 h threshold was prioritization of motor rehabilitation over speech).

A 2012 Australian pilot study randomized 59 subjects to daily ST, beginning mean 3.4 days after stroke, or SC [70]. Most SC subjects received no ST during the intervention period. Primary outcome was Western Aphasia Battery Aphasia Quotient (WAB-AQ) at discharge from acute rehabilitation or 4 weeks post-stroke, whichever came first. In this trial, 81% of subjects in the intervention group met the pre-specified minimum therapy goal of 2.5 h, with a median of 4.75 h of total therapy over the course of the study, compared with 48 min in the SC group. The trial was positive; accounting for baseline aphasia severity, subjects in the intervention group scored 15 points higher on the WAB, a difference considered clinically meaningful. This group is currently conducting a phase III trial, VERSE (Very Early Rehabilitation of Speech) [71], with a projected sample size of 246 patients, which once completed will displace RATS-3 as the largest aphasia recovery trial.

In 2013, the same group conducted another small study [72], in which they compared Constraint-induced Aphasia Therapy (CIAT), a structured group therapy modality fashioned after CIMT, to individual therapy. Subjects were enrolled within 7 days of stroke and were randomized to one of the two treatment paradigms, which were delivered at the same intensity (45–60 min/day, 5 days per week, for 4 weeks). The trial did not demonstrate superiority of CIAT over traditional therapy; both groups experienced significant improvement in WAB-AQ, but without a control group, the contribution of spontaneous improvement could not be assessed. The researchers also published a pooled analysis of the two trials above, designed to investigate the question of a dose-response effect [73]. They found that in a regression model, amount of therapy predicted recovery—for every 10 min increase in therapy, AQ improved by 6.3 points.

Another very small RCT ($n = 12$) also found benefit of ST in the early time window, comparing intensive individual ST (1 h/day, 5 days/week for 2 weeks), beginning on average 2 days post-stroke, to no therapy [74]. The primary clinical endpoint was the Aachen Aphasia Test (AAT) post-treatment. The intervention group had significantly greater gain in AAT domains of naming and writing, a difference which persisted at 6 months. This study also investigated the neural underpinnings of recovery using serial fMRI. At baseline, all subjects showed markedly reduced activity throughout the language network. At 2 weeks, differences emerged, with the intervention group showing increased activation in critical left-hemisphere language regions, particularly left inferior frontal gyrus (IFG; Broca's area). Activation in left IFG correlated with naming performance, and between-group differences persisted at 6 months, providing preliminary evidence that early language rehabilitation can promote beneficial cortical reorganization.

Finally, Conklyn et al. investigated the effect of Melodic Intonation Therapy (MIT), a language therapy designed to take advantage of aphasic people's relatively preserved ability to sing [75]. The study enrolled 30 subjects with Broca's aphasia within 14 days of stroke. A significant between-group difference in language production was seen after a single session of MIT, measured on a proprietary repetition and spontaneous speech task. This study must be interpreted with caution, as the clinical relevance of the outcome and the durability of improvement are not known, but it does provide proof-of-concept that MIT can be delivered successfully in the first days after stroke and may be beneficial.

In summary, given the negative RATS-3 trial, there is a lack of clear evidence that early ST in aphasic stroke patients is beneficial. However, it should be noted that the positive Australian study had a higher percentage of patients with severe aphasia than RATS-3, and commenced therapy about 5 days sooner. The ongoing VERSE trial should help to clarify whether very intense therapy does provide benefit, as suggested by the RATS-3 post hoc analysis, especially in the most severely aphasic patients.

Neglect

Our search identified three recent RCTs of treatments for unilateral visuospatial and/or motor neglect early after right hemisphere stroke. The first trial studied right hemifield eye patching (HEP) in subjects within 15 days of stroke [76]. Patching is designed to redirect attention to the neglected hemifield by obscuring the normal field via opaque patches worn on glasses. Subjects in the intervention group wore patches for 8 h per day for 15 days and received no other specific therapy for neglect. The control group received "standard" visual scanning therapy every weekday for 15 days. No significant differences were seen between the groups on the neglect outcome battery (line bisection, line crossing, Bell cancelation). The trial's neutral result can be interpreted in different ways; it can be taken to show that HEP has no advantage over standard therapy, or that HEP, a passive intervention that costs virtually nothing, is as effective as individual therapy. A second trial [77] tested the hypothesis that HEP should be combined with active therapy. Patients were randomized within 14 days of stroke to either HEP plus optokinetic stimulation or SC. Here too, no difference was seen between the two groups, both of whom showed marked improvement, in keeping with previously reported high rates of spontaneous recovery of neglect [78].

Finally, the Mirror Therapy in Unilateral Neglect After Stroke (MUST) trial [79] tested the efficacy of mirror therapy for hemispatial neglect in 48 patients enrolled within 48 h of stroke. Patients received either mirror therapy or sham immediately prior to standard OT for 1–2 h/day, 5 days/week for 4 weeks. This study was positive, finding significant improvement in the intervention group compared with controls on neglect outcomes: star cancelation, line bisection, and picture identification. The treatment group also had significantly greater FIM scores at 3 and 6 months post-treatment.

In sum, the current evidence does not support the use of hemifield patching in the acute phase of stroke, but mirror therapy may be a promising treatment. The HEP trials highlight the need for biomarkers to better predict the course of neglect in individual patients—given the high rate of spontaneous resolution of neglect, in order to prove the benefit of early interventions, we need methods to predict who is likely to recover spontaneously and who is not.

Dysphagia

We found three recent trials of early post-stroke dysphagia therapy, two testing novel treatment paradigms, and one addressing the question of optimal timing of therapy initiation. One investigated neuromuscular electrical stimulation (NMES) of the infrahyoid region for patients within 10 days of supratentorial stroke with dysphagia, and found benefit of NMES over SC on the Functional Oral Intake Scale (FOIS) at 3, 6, and 12 weeks, as well as in the likelihood and speed of resuming oral feeding [80]. Limitations of the trial include small sample size and high rates of spontaneous recovery. Another trial investigated rTMS for acute post-stroke dysphagia [81]. Patients were enrolled at median 8 days from stroke and randomized to one of three arms: high-frequency (3-Hz) stimulation of the lesioned hemisphere, low-frequency (1-Hz) stimulation of the non-lesioned hemisphere, or sham rTMS. The trial tested both excitatory and inhibitory stimulation paradigms on the theory that dysphagia, like many post-stroke deficits, is driven at least in part by an imbalance between the two hemispheres (i.e., overactivation of the unlesioned hemisphere causing suppression of the lesional side), and that either method of restoring hemispheric balance could be beneficial. Significantly greater improvement was seen on the Standardized Swallow Assessment in both rTMS groups compared with sham, both immediately post-treatment and at 1, 2, and 3 months. Neurophysiologically, 1-Hz rTMS decreased cortical excitability of the unlesioned hemisphere and increased excitability in the lesional hemisphere. 3-Hz rTMS increased excitability of the lesional hemisphere and did not significantly affect the unlesioned hemisphere.

Finally, Bakhtiyari et al. randomized patients to begin swallow therapy at one of three time points: early (≤ 3 days), medium (≤ 14 days), or late (≤ 30 days) [82]. They found a significant interaction between early group assignment and swallow recovery; rates of aspiration measured by the North-Western Dysphagia Patient Check Sheet post-treatment were 5% in the early group, 20% in the middle group, and 30% in the late group ($p = 0.043$). Interpretation of these results, however, is confounded by the fact that subjects randomized to late treatment were excluded if they recovered completely prior to beginning therapy.

Thus, much of the good outcome in the early intervention group could have been driven by spontaneous improvement.

Commentary

This review brings to light several important themes for the future of stroke recovery research. The first is a pattern seen across medical research, namely, that seemingly promising findings from small trials are exceedingly difficult to reproduce in larger trials. This problem is especially apparent in the rehabilitation literature, where most trials are small, single-center, pilot studies, and steady, incremental progress from proof-of-concept studies to multicenter trials is lacking. The AVERT experience is illustrative; that 2100-person trial was predicated on three small RCTs, which collectively enrolled 159 patients, with a pooled analysis showing the intervention to be safe with a non-significant trend toward benefit [83]. From that arguably shaky base, the AVERT investigators proceeded with a large and ambitious phase III trial, which not only failed to prove the efficacy of the intervention, but demonstrated harm. Likewise, in the realm of aphasia, the recently published negative RATS-3 trial was based upon neutral preliminary data—the RATS-2 pilot study found no significant between-group differences, but a trend toward benefit in the intensive ST group on 2/6 language subtests was interpreted as sufficiently promising to spur investment in the larger trial [84]. Meanwhile, very small trials of novel interventions proliferate, and some appear promising, but most are never reproduced and never progress to multicenter studies. Investigators in this space would do well to view preliminary results with a highly critical eye, focus on mechanisms, and consider novel trial designs, such as adaptive designs, to move promising ideas forward without committing massive resources to ideas that lack true proof-of-principle basis.

Another challenge that emerges in this review is lack of consistency in the selection of outcome measures, which was seen across all the domains we surveyed. While the mRS has many shortcomings as an outcome measure, its near-universal adoption in acute stroke trials has made it possible to easily compare trials and to perform meta-analyses, a crucial tool for increasing the power of small trials. In the recovery world, outcome measures abound, and while researchers can make keen arguments in favor of their chosen metric, the lack of common standards clearly muddies the field.

Yet another challenge in early rehabilitation research derives from the inherent heterogeneity of stroke patients. Recovery after stroke is known to be highly variable. Numerous factors—some known (e.g., age, lesion size and location, stroke severity, medical comorbidities) [85–88], and many unknown—affect recovery at an individual level. As other experts have observed, development of biomarkers and other tools to reliably stratify patients by recovery potential early in the course of stroke would be of enormous benefit to future trialists [89]. We saw in the EXPLICIT trials that when a metric of recovery potential was used to stratify patients, the trial was able to detect a benefit of an intervention that was not seen in other, undifferentiated populations.

Finally, several studies examined the impact of early rehabilitative interventions on cortical excitability and all detected changes in brain plasticity related to the intervention. In many

cases, these plastic changes did not translate into functional gains. Nonetheless, research using tMS, fMRI, positron emission tomography (PET), or other novel tools such as high-density array EEG [90, 91] to understand how rehabilitation changes brain function after stroke is of great value in advancing the scientific underpinnings of the field and may aid in designing successful trials.

Conclusions

As this review makes abundantly clear, the optimal timing to begin rehabilitation after a stroke is still not known. There is mounting evidence that rehabilitation within the first 24 h, especially intensive rehabilitation, is potentially harmful, and we would advise caution in pursuing further investigations of intensive rehabilitation within this timeframe. Beyond 24 h, rehabilitation of diverse types appears to be safe, but a well-defined “plastic window” in humans, during which injured brain is particularly primed for rehabilitative intervention, remains elusive. The best results in the early time window have been seen in upper extremity CIMT studies. It is highly plausible that early intervening to prevent learned overuse of the unaffected side impacts cortical reorganization in a beneficial way. In contrast, early interventions for aphasia have so far been disappointing. We await results of the ongoing VERSE study, but current evidence suggests that in undifferentiated aphasic patients, merely beginning standard ST earlier has no meaningful impact on long-term language outcomes. In the realms of dysphagia and neglect, early intervention has shown some promise, but the evidence is limited, and the high proportion of spontaneous recovery makes it difficult to assess the true impact of early intervention.

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