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Strategies for Early Stroke Recovery: What Lies Ahead?

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Opinion statement

Most patients experience some degree of recovery after a stroke, but the majority of patients still have persistent impairments months later. Most recovery occurs early after a stroke, in the first few weeks to months, corresponding to a period of enhanced neuroplasticity. We are beginning to understand the mechanisms that underlie this recovery process, and how we can take advantage of this plasticity in designing rehabilitative interventions. In this review, we focus on recent behavioral, pharmacological, and brain stimulation strategies that have shown promise in augmenting stroke recovery. Several studies, both in animals and humans, suggest that early initiation and high doses of therapy are crucial for maximizing the benefits of rehabilitation. The investigation of early and intensive therapy in clinical trials has been limited, likely due to the logistical challenges of conducting such studies. Other strategies for promoting recovery seek to modulate neuroplasticity or to enhance the effects of rehabilitation, including the use of pharmacological agents, stem cell therapy and non-invasive brain stimulation. While there has been recent growth in stroke recovery and rehabilitation research, there is still a great need for more basic science and clinical research to further our understanding of the stroke recovery process and develop optimal rehabilitative strategies for promoting stroke recovery.

Introduction

Stroke is a leading cause of long-term disability, with many patients experiencing persistent cognitive, motor, sensory and visual impairments [1]. While the focus of clinical care and research has been primarily on acute stroke reperfusion therapy, recent progress in our understanding of the neural processes that underlie stroke recovery, and the interaction between behavioral experience and those recovery processes, have led to

rapid growth in neurorehabilitation research. Strategies for enhancing post-stroke recovery through rehabilitation and adjunctive interventions are areas currently under investigation. In this paper we review the major concepts and strategies in the development of behavioral therapies for stroke rehabilitation, as well as some pharmacological and brain stimulation interventions that have emerged as potential therapeutic strategies for enhancing early stroke recovery in recent preclinical and clinical studies.

Neuroplasticity after stroke

After a stroke, there is a "sensitive period" of enhanced neuroplasticity [2, 3••, 4••]. Most recovery of stroke-related impairment occurs early, during the first three months after a stroke, according to human studies [3••, 5, 6]. Mechanisms that contribute to this spontaneous recovery include restitution of penumbral tissue, resolution of edema, reversal of diaschisis and, most importantly, neuroplasticity [7]. Stroke results in the loss of tissue in the infarct core, but also to cellular and molecular changes that lead to brain reorganization in the peri-infarct region and more remote areas that have connections to the infarcted region.

In response to the acute injury, there is an upregulation of both growth-promoting and growth-inhibiting processes that contribute to poststroke plasticity [2, 8]. Genes involved in synaptogenesis, neuronal growth, axonal sprouting and dendritic spine development are upregulated in peri-infarct areas [2, 4••]. There is also upregulation of inhibitory processes that may serve to limit excitotoxicity and maladaptive plastic changes after stroke [4••, 9]. These repair-related processes lead to a time-dependent window of enhanced neuroplasticity after stroke [3••, 10••].

Behavioral therapies to enhance recovery

The goal of neurorehabilitation is to provide behavioral training that will lead to a reduction in stroke-related impairment and improve long-term functional outcomes. We have learned of several important ways for enhancing the effect of training from previous research with animals. We know that training is important for neuroplasticity after stroke, as shown in a series of experiments in primates after a motor stroke [11, 12]. With upper extremity training, there was an expansion of distal forelimb representation in the peri-infarct cortex associated with behavioral recovery, whereas, without training, there was loss of distal forelimb representation. The optimal timing, intensity and type of rehabilitation for improving stroke recovery in humans have not yet been established, however.

The effects of training after stroke are generally greater when started early after stroke, perhaps because we can take advantage of the "sensitive period" of enhanced neuroplasticity. Rats that were exposed to an enriched environment, together with intense reach training therapy beginning five days after a stroke, showed more improvement than animals that started rehabilitation later; when the rehabilitation was delayed by 30 days, the animals showed no improvement over the control group that did not receive any training [13]. The behavioral improvements seen with early rehabilitation were ac-

companied by increased dendritic branching in the peri-infarct motor cortex, which was not seen with delayed rehabilitation.

Despite the general acceptance that mobilization and rehabilitation should be started early after a stroke [14], most of the randomized clinical trials of behavioral interventions have been conducted with chronic stroke patients (i.e., >6 months post-stroke) [15]. Logistical challenges to conducting early clinical trials of rehabilitation include recruitment and compliance with frequent follow-up visits, because patients are often still hospitalized in acute rehabilitation units or receiving therapy as part of their clinical care. Another reason for the historical emphasis on the chronic stroke population is that the patients have reached a stable baseline, so it is easier to see the effect of an intervention. However, recovery does not appear to be as variable as once thought; more recent studies suggest that the degree of recovery can be predicted by the severity of the initial impairment, at least in some domains. We have shown, for example, that for most patients, the degree of motor recovery in the upper extremities in the first three months has a proportional relationship to the degree of initial impairment, with patients recovering approximately 70 % of their initial motor impairment [16]. A similar proportional relationship was found for recovery of language impairment [17]. If recovery is predictable, it should then be possible to conduct studies in this early three-month period after a stroke by comparing the recovery trajectories for an experimental intervention group and a non-intervention control group that will presumably follow this proportional recovery course.

There have been a limited number of studies investigating the effects of early behavioral interventions after a stroke. There has been concern regarding the safety of high intensity therapy during the hyperacute post-stroke period in that it may promote excitotoxicity and infarct expansion [18]; however, early and intensive therapy in preliminary clinical trials has proven to be feasible and well-tolerated [19–21]. In the VECTORS study of early constraint-induced movement therapy, the group that received higher intensity constraint-induced movement therapy (CIMT) had less improvement at day 90 than the lower intensity CIMT group, but there was no evidence of activity-dependent lesion expansion seen in the MRI substudy [19]. Mobility training within 24 hours after a stroke was found to be safe and led to an earlier return to ambulation and better functional outcomes compared to standard care outcomes [20]. A phase III study of early mobilization is currently underway. Early aerobic exercise is yet another intervention that may improve early recovery from stroke. In animal stroke models, high intensity aerobic exercise was associated with neuroplasticity, producing enhanced neurogenesis and angiogenesis [22].

The optimal levels (i.e., dosage) of rehabilitation therapy after a stroke have yet to be established. Studies of training-induced plasticity in healthy animals and humans show that behavioral improvements and accompanying neuroplasticity require a lot of practice. Animal studies that have shown the benefits of training result from very high levels of therapy, typically 300 repetitions per day on a particular task [3••]. Greater gains have also been shown in cases where animals have unlimited access to enriched environments, where they can participate in various activities and where they can socialize with other animals [13, 23].

A recent meta-analysis reviewed the effect of dosage (defined as time scheduled for therapy) on the magnitude of functional improvement in human studies and found a positive dose-response relationship [24]. The effect of time following a stroke was not significant in this meta-analysis, possibly

because the majority of studies included in this analysis were conducted on patients who were within one year of their stroke. Furthermore, the inclusion of studies broadly encompassing different functions and impairments makes it difficult to draw conclusions about the extent of true recovery versus functional compensation [19, 25]. Studies that directly investigate the effect of dosage at different times after stroke are needed to further examine the post-stroke interaction of dosage and time.

The goal of achieving a high dose of therapy in human rehabilitation is a challenging one. For motor rehabilitation, robotic therapy is a promising intervention that can deliver high intensity therapy with over 1,000 repetitions per session [26•], far greater than what is typically delivered in a conventional therapy session [27]. Robotic therapy also has other advantages for rehabilitation. It can provide titrated degrees of assistance for patients who are unable to fully move on their own and who may be too severely impaired for other techniques such as constraint-induced movement therapy. It can also be paired with a game that can be made to incorporate goals and feedback, factors that are important for motor learning and for motivating patients to be compliant with their therapy. Another feature of robotic therapy is that the devices have the capability of taking measures during therapy, so that we can learn not just if, but how, patients are improving with training.

Studies of robotic therapy in chronic stroke patients have shown modest benefits. A meta-analysis of randomized clinical trials of robotic therapy in chronic stroke patients found a significant improvement in upper limb motor impairment scores, but not in activities of daily living [28]. In the Veterans Affairs (VA) ROBOTICS study, the largest robotic study to date, patients with residual arm impairment after chronic stroke were randomized for robotic therapy, intensity-matched conventional therapy and usual care [26•]. After 12 weeks of therapy, there was no significant difference in upper limb impairment scores in the three groups. Secondary analyses at 36 weeks showed greater improvements with robotic therapy than with usual care, but not over intensity-matched conventional therapy. One criticism of these previous robotics studies is that most utilized two-dimensional movements during therapy, which are not ecologically meaningful. A more recent study of upper limb robotic therapy using the ARMin device, which is capable of three-dimensional movements, also showed a small improvement in motor impairment with robotic therapy compared with time-matched conventional therapy [29]. The benefits of robotic therapy in both of these randomized controlled studies was small and of questionable clinical significance. As with most rehabilitation studies, these were conducted with chronic stroke patients, and it has been surmised that earlier therapy administered during the sensitive period may achieve larger effects. A recent study in 53 patients with subacute stroke found decreased spasticity and increased range of motion with robotic therapy compared with time-matched conventional therapy, but no difference in improvements in motor impairment scores [30].

Pharmacological and cell-based therapies

Pharmacological interventions have a long history of clinical trials, with mixed results. Selective serotonin reuptake inhibitors (SSRIs) have been commonly used to treat poststroke depression and have been recently studied for their beneficial

effects on poststroke recovery. The exact mechanisms of SSRI effects on recovery are still being investigated, but may include the promotion of angiogenesis [31], neurogenesis [32] and anti-inflammatory effects [33].

In a multi-center, double-blinded randomized clinical trial, patients who received fluoxetine beginning 5-10 days after a stroke had greater motor recovery, and a higher proportion of patients were independent (mRS scores 0-2) after 90 days, compared to those who received a placebo (FLAME trial) [34•]. This effect was present even after adjusting for clinical depression. The benefits of SSRIs after stroke are also supported by a meta-analysis of 52 trials using SSRIs for any indication in the first year after stroke [35]. They found that patients who received SSRIs were less likely to be dependent (mRS >3), disabled or neurologically impaired. Patients who received SSRIs were also less likely to be depressed or anxious, but subgroup analysis of patients who were not depressed at study onset also showed a benefit of SSRI treatment. However, there was substantial heterogeneity in patient characteristics, timing of administration and outcome measures.

While the results of the FLAME trial and other smaller studies are promising, the benefits of SSRIs on functional recovery still need to be further established to support their routine use in poststroke care. Potential side effects also include risk of cerebral bleeding due to their effects on platelets [36]. Currently there are several larger trials of SSRIs for poststroke recovery that will further evaluate the clinical benefits of early SSRI administration on functional recovery, including the *Fluoxetine or Control Under Supervision* (FOCUS) trial, the *Australasian Assessment of Fluoxetine in Stroke Recovery* (AFFINITY) trial and the *Effectiveness of Fluoxetine – a Randomized Controlled Trial in Stroke* (EFFECTS) trial.

Several other pharmacological agents are being investigated for enhancing poststroke recovery in preclinical studies. Memantine, a N-methyl-D-aspartate antagonist used to treat Alzheimer's disease, was recently found to have benefits for motor recovery in a mouse stroke model [37]. In this study, mice that received memantine for 28 days beginning 2 hours after an experimental stroke showed greater improvements in the impaired forelimb control, compared with mice who were given a vehicle alone. The infarct size, stimulation maps and behavior were not significantly different between the two groups in the first week after the stroke, however, suggesting that the effect of memantine was not neuroprotective, but rather related to recovery. Treatment for 28 days was associated with improved motor outcomes, decreased reactive astrocytosis, increased vascular density and increased brain-derived neurotrophic factor (BDNF).

With advances in our ability to grow and deliver stem cells to brain tissues, cell-based therapy is also emerging as a potential approach to stroke recovery. The initial aim of stem cell therapy was to introduce new cells that would form new circuitry after a stroke; however, in animal studies to date, the mechanism by which stem cells exert their effect on recovery appears to be through a bystander effect, through promotion of neuroplasticity in endogenous cells. This effect includes secretion of growth factors, promotion of angiogenesis and modulation of the inflammatory response after a stroke [38–40]. In preclinical studies, stem cells have been shown to migrate to the peri-infarct region and participate in upregulation of growth-promoting factors, including BDNF, vascular endothelial growth factor (VEGF), nerve growth factor (NGF) and basic fibroblast growth factor (bFGF), among others. Stem cell therapy also has been demonstrated to reduce functional

deficits when administered early after a stroke in animals [41–43]. While animal studies have been promising, cell-based therapy for stroke recovery has only recently begun to be tested in small clinical studies. These initial clinical trials of stem cells demonstrate that the therapy is safe [44–46], though their efficacy for functional post-stroke recovery remains uncertain.

Non-invasive brain stimulation

Transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) are non-invasive brain stimulation techniques that have emerged as potential ways to augment recovery by modulating brain excitability after a stroke. The use of brain stimulation in stroke recovery is based upon findings of altered brain excitability after a stroke. Neuroimaging studies have demonstrated altered patterns of brain activation in stroke patients. For example, movement of the affected hand is associated with bilateral activation of motor areas [47–49]. Patients with good recovery often reacquire lateralized activation/excitability of the lesioned side, similar to the activation patterns seen in healthy control subjects, whereas patients with poorer recovery have shown persisted activation of the contralesional hemisphere [47, 48]. Electrophysiological studies have also demonstrated a disruption of the usual balance of excitability between the two hemispheres, with abnormally high inhibitory input from the unlesioned to the lesioned hemisphere [50, 51].

Depending on the parameters of the stimulation, the effects of TMS and tDCS can be facilitatory or inhibitory [52]. TMS and tDCS have been used to increase excitability of the lesioned hemisphere and to suppress excitability of the contralesional hemisphere. Small studies of rTMS and tDCS paired with behavioral therapy, mainly in chronic stroke patients, have demonstrated improvements in motor performance [53–56], aphasia [57–60] and neglect [61•, 62]. Dual hemispheric stimulation, with excitatory stimulation of the lesioned hemisphere and inhibitory stimulation of the contralesional hemisphere, combines these two strategies.

A recent study investigated the effects of dual hemispheric rTMS for early treatment of post-stroke aphasia [63]. Thirty patients were enrolled within 12 weeks of their stroke, and randomized to 10 sessions of real or sham dual hemispheric rTMS, with stimulation over the left Broca's area and the homologous area on the right, immediately preceding speech and language training. Here they found overall greater improvements in language and depression scores with real rTMS compared with sham stimulation. Interestingly, some patients in this study with severe aphasia and extensive infarction showed no behavioral improvement with the combined rTMS and speech-language therapy, suggesting a limitation by severity or lesion volume, and demonstrating that patient selection is an important factor to consider in designing future clinical trials.

Not only patient selection, but timing of the intervention, optimal sites of stimulation and the optimal parameters for stimulation remain unanswered questions for the use of noninvasive brain stimulation. Functional imaging has been used to guide selection of patients based on sites of activation and degree of interhemispheric activation, but we do not know whether these imaging markers can distinguish patients who are most likely to benefit from stimulation. As with other interventions, most studies of noninvasive stimulation have been conducted in chronic stroke patients, but

studies have demonstrated benefits in the early stroke period as well [64, 65]. Because of ongoing neuroplasticity during the recovery process, however, optimal sites of stimulation may change depending on the timing of therapy post-stroke. Finally, recent studies have generally simply replicated the stimulation parameters used in previous stimulation studies now over a decade old. Systematic investigations are needed to determine the differential effects of stimulation intensity, duration and frequency on changes in cortical excitability and functional recovery.

Conclusions

Recent advances in our knowledge of neuroplasticity after a stroke and findings from animal studies of post-stroke recovery suggest promising strategies for enhancing the recovery process. Behavioral interventions should be intensive, motivating and be administered early enough to take advantage of the early sensitive period of enhanced post-stroke neuroplasticity. There is also potential for enhancement of this plasticity through pharmacological agents and non-invasive brain stimulation. In order for the field of neurorehabilitation to adopt these strategies on a widespread scale, however, we need more evidence-based data from clinical trials, particularly in the early period after a stroke.

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Compliance with Ethics Guidelines

Conflict of Interest

Dr. Tomoko Kitago declares no potential conflicts of interest.
Dr. Randolph S. Marshall declares no potential conflicts of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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