Novel Stroke Rehabilitation Interventions

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Stroke is a major cause of neurological impairment; over half of stroke survivors have persistent upper limb impairment, and 25-50% of stroke survivors have persistent moderate to severe disability, especially in the realms of motor and language functions after completion of standard rehabilitation.[1] The prevalence of stroke survivors was over six million in 2006,[2] and is expected to increase as the population ages despite advances in stroke prophylaxis and acute treatment such as tPA. There is a pressing need to improve the neurologic function of stroke survivors.

The neurorehabilitation interventions employed by physical, occupational, and speech therapists on a practical level have changed little over the last 40 years. This is not for lack of trying. Determining efficacy of traditional and novel interventions has been hampered by methodological challenges including heterogeneous functional neuroanatomy and neuropathology, inadequate outcome measures (subjective, questionable ecological relevance), and logistical difficulties in studying a population with disabilities (impaired mobility and increased risk of medical problems to name only two which cause study subjects being easily lost to follow-up).

Fortunately, recent progress in neuroscience, particularly the discovery that the adult brain has surprising potential for plasticity especially after injury; and in the development of new technologies (computer science, biomechanics, cell and tissue manipulation, neuropharmacology) have driven the development of multiple promising interventions which could improve the function of those with neurological impairments.

Efforts are underway worldwide to determine how these techniques can be applied clinically. Critical questions include: which patients are most likely to benefit from interventions? Are there certain windows of opportunity during which an intervention would be most effective? Should different interventions be utilized in certain sequences?

Until recently the prospect of being able to answer these questions scientifically in a reasonable period of time was fantasy. However, new tools and novel techniques such as functional imaging and relevant surrogate outcome measures are helping to rapidly answer many of these questions and improve our understanding of neurological recovery.

We describe some of the most promising new restorative interventions for stroke rehabilitation currently being investigated. (Compensatory approaches, such as brain-computer interfaces, are beyond the scope of this paper.) Some, or all of them may, in some form, become standard components of neurorehabilitation programs in the coming years. Many of these techniques are being investigated for the rehabilitation of other neurologic conditions (TBI, MS, Parkinsons, etc.) but this report focuses on stroke.

Robotic Therapy

One of the exciting developments in stroke rehabilitation is the emergence of rehabilitation robots.[3-4] Robots have a number of attractive inherent capabilities, ranging from the tireless ability to facilitate precise repetition of movement in multiple planes to the inclusion of integrated instrumentation, allowing kinematic analysis and feedback for performance. There have also been an incredible variety of robots that target impairment of the upper-limbs, lower limbs, or specific joints (such as the Anklebot[5]); devices that train movement unilaterally or bilaterally using exoskeleton systems or end-effector devices.

However, in parallel to the amazing technological developments, rigorous clinical testing is critical to evaluate safety and efficacy. To date there have been a number of pilot studies but very few large randomized controlled trials. The largest robot trial has been the **ROBOTICS study (Robots in Chronic Stroke)** conducted by the Department of Veterans Affairs.[6, 7] This study investigated the safety and efficacy of the MIT-Manus device (Figure 1) among 127 subjects with chronic upper extremity impairment following stroke. In addition to robot therapy, the study included an active treatment group that used conventional rehabilitation techniques. Although both groups showed improvement over the 36 week period of the study, there was no clear treatment advantage of robot over matched therapy using conventional methods.[8]

Most other smaller studies using upper-extremity devices have had similar results, such as with the T-Wrex (Figure 2).[9] A recent report has described ben-

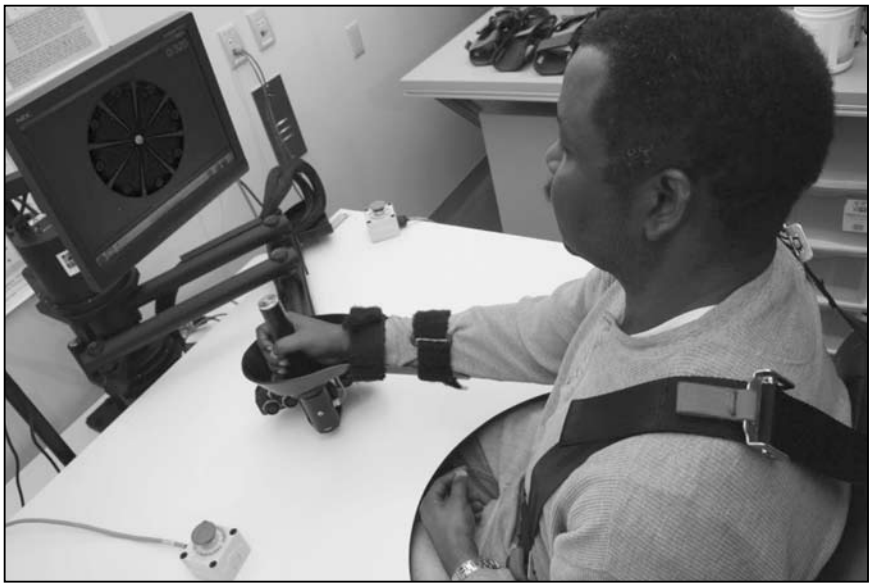

Figure 1: Manus Device

eficial results from the REO Therapy System for inpatients during the subacute timeframe.[10] Randomized studies focusing on the lower extremities using robotic-assisted gait training (Lokomat) (Figure 3) compared to conventional gait training, also have not shown advantages to the robot-based protocol on clinical outcomes.[11]

Nevertheless, rehabilitation clinical trial testing is evolving and it still may be a matter of identifying the optimal manner and environment to use robot technology. For example, enhanced use of feedback, or integration with virtual reality or telerehabilitation may be other promising strategies for robotic devices. Technology will continue to develop and robots should be viewed as tools with unique strengths and functions which must be optimized for their most appropriate clinical applications. Costs for robotic devices, which range from tens of thousands to $300,000, will also have to be greatly reduced in order for robots to be used commonly in clinical rehabilitation. In the broader scheme, robots like other tools must be used to their best advantage to investigate the critical questions of rehabilitation such as when to intervene with activity-based therapies, what are the appropriate doses and intensities, and how do we best track and predict treatment-responsiveness.

Constraint-Induced Movement Therapy (CIMT)

This technique is based on the concept of *learned nonuse* advanced by Taub in the 1970s, and first examined in nonhuman primates,[12,13] in which use of an impaired limb is suppressed presumably by the finding that compensatory strategies are easier to utilize than relearning use of the affected limb. Taub postulated that *forced use* of the impaired limb and/or *prevention of use* of the non-affected limb could enhance functional recovery of the impaired limb. These principles were then adapted to human subjects with hemiparesis due to stroke.[14]

The classic CIMT paradigm involves intensive repetitive practice of use of the affected limb under the direct, continuous supervision of a therapist on a one-on-one basis for up to six to seven hours a day for at least two consecutive weeks while the better arm is prevented from being used (by using a sling or a mitt) for 90% of waking hours. Initial studies generally showed long-lasting benefits on various motor and real-world functional measures, but lack of vigorous control groups and small *N* were concerns. EXCITE, a multicenter, randomized, controlled trial, confirmed the effectiveness of the technique when applied rigorously in patients who are strongly motivated, have preserved cognition, and have some isolated movement present at the wrist before treatment.[15] Functional imaging studies suggest CIMT therapy is associated with cortical reorganization in areas involved in control of the affected limb. It is unclear if the mechanism of benefit is the mass practice of use of the affected limb alone vs. constraint of the other limb vs. both.

The classic paradigm, however, has not come into widespread use, as CIMT is expensive to administer due to the large amount of therapist time required and is generally not covered by insurance. In addition, some patients find it frustrating and overwhelming. The classic technique is limited to patients who fit criteria, which excludes more severely hemiparietic individuals.

As a result, several "**modified**" **CIMT** (**mCIMT**) trials have been run, involving less therapist time with more practice at home, less constraint on the other limb, and more liberal inclusion criteria. Some of these trials suggest that mCIMT paradigms could result in enhanced patient compliance, greater use, and be less expensive, while remaining effective.

In addition, the concept has been successfully applied to other stroke sequelae such as lower limb sensorimotor impairments and aphasia, as well as other diagnoses such as traumatic brain injury, spinal cord injury, focal dystonia, and phantom limb pain. It has also been applied in pediatric populations, particularly for cerebral palsy.

Classic CIMT is currently done only at highly specialized centers such as University of Alabama at Birmingham where the technique was developed. However, many therapists incorporate mCIMT into their treatment designs, and some centers are running mCIMT programs.

Pharmacological Interventions

Another potential approach to enhancing spontaneous plasticity for restoration of poststroke neurological function is the use of medications.[16] Studies have been small, in selected populations and have had mixed results. Such studies are methodologically challenging, but the advent of functional imaging and genetic techniques may allow better characterization of involved neurotransmitter pathways which could in turn enhance the design of clinically useful studies.

It may seem intuitive that increasing the activity of a neurotransmitter system whose activity has decreased after a stroke, or vice versa, could be beneficial, but careful study is needed to ensure safety and to determine when agents will be most useful in which patient populations. In addition to direct clinical applications,

Figure 2: T-Wrex Device

studying the effects of such drugs could provide insight into the effects of stroke on specific neurotransmitter systems.

Most clinical studies have evaluated the effects of drugs on motor function and aphasia.

A discussion of several of these drugs provides a sense of the current state of knowledge. This is not a complete list of pharmacologic approaches to enhance stroke recovery. It is likely that medications will need to be used in combination with physical therapy or mass practice in order to produce a beneficial effect. Appropriate patient selection based on various parameters (e.g. clinical impairments, stroke size and location, and time elapsed since onset), is an additional challenge.

d-Amphetamine and other stimulants

The theoretical action of amphetamine is its enhancement of the synaptic release of two neurotransmitters that support motor function, dopamine and noradrenaline. In a rat model, treatment with amphetamine, an enriched environment, and/or focused motor activity resulted in better motor function than controls, and treatment with all three showed the most robust recovery.[17]

Although some human studies have shown beneficial effects of d-Amphetamine, other studies have not. A 2007 Cochrane review concluded that its potential role in motor rehabilitation is unclear due to conflicting results in trials thus far.[18] Barbay and Nudo suggest that the better apparent results in animal vs. human studies may be attributable to uncertainty of optimal dosage and timing of administration.[19] A 2009 review of eleven trials noted an overall trend toward improved motor function, but raised concerns about safety particularly with respect to hemodynamic effects, and concluded that "No evidence exists at present to support the use of amphetamine after stroke."[20]

There have been a few studies of other stimulants in stroke. Methylphenidate (increases dopamine signaling), when combined with physical therapy, was shown to have a beneficial effect on motor outcomes and decreased depression. This drug has been better studied in TBI, with evidence that it may improve mental processing speed and reduce both ICU and hospital length of stay.[21]

Figure 3: Lokomat device

Selective Serotonin Uptake Inhibitors (SSRIs)

Studies in animal stroke models have suggested potential mechanisms by which SSRIs could enhance recovery.[22] In a study of severely disabled chronic stroke patients, ambulation and activities of daily living improved more in those treated with fluoxetine 20 mg daily than in those treated with 150 mg maprotiline (a tetracyclic antidepressant) or placebo.[23]

Another study found fluoxetine treatment to be associated with improvement in motor skills which correlated with changes in activation patterns on functional MRI.[24] In a small controlled trial, a single dose of citalopram 40 mg resulted in greater improvement in upper-limb dexterity but not grip strength in the affected, but not the unaffected, hand.[25] These studies suggest that SSRIs may have a measurable physiologic effect specific to areas important to post-stroke recovery of motor function, implying a mechanism other than antidepressant effects may be responsible for gains in motor function.

A larger (N = 118) multicenter randomized controlled trial of fluoxetine in chronic stroke demonstrated significantly greater improvement in motor function in subjects treated with fluoxetine 20 mg daily compared to placebo, and the treatment was well-tolerated.[26]

Of note, preliminary retrospective reports suggest that SSRIs could increase the risk of stroke.[27] SSRIs are a promising class of drugs to enhance recovery of motor function in chronic stroke patients but further study is necessary to inform risk:benefit ratios before widespread clinical use can be considered.

Phosphodiesterase type-5 Inhibitors (PDE-5I)

PDE-5I's are approved for use for the treatment of erectile dysfunction and idiopathic pulmonary arterial hypertension. However, the indications may broaden to treatment of cardiovascular, gastrointestinal, cutaneous, and neurologic disorders. They may be useful in Raynaud's phenomenon, heart failure, essential hypertension, and stroke.[28]

Cyclic **guanosine monophosphate** (**cGMP**), which increases with sildenafil citrate administration, increases neurogenesis, angiogenesis, and synaptogenesis in animal models of stroke.[29] A rat model of stroke suggests improvement in functional recovery and neuronal function due to modulation of microglial function and/or vasculature.[30]

An atypically good recovery without adverse effects was reported in a 41 year-old woman with locked-in syndrome due to a pontine stroke who was treated with sildenafil for several years.[31] The remarkable case of a 65-year-old man with chronic stroke whose residual bilateral inferior quadrantanopia reproducibly and

verifiably improved for three to seven days each time he took a dose of sildenafil 25 mg was recently reported. Functional MRI showed sildenafil-associated activations at the infarction periphery.[32] Silver et al found sildenafil to be safe when given for two weeks starting two to nine days after onset of mild to moderately severe stroke in a small trial.[33]

These and other preliminary reports, which suggest possible safety and efficacy along with functional imaging suggesting corresponding cortical effects, indicate that further investigation of the use of PDE-5I in rehabilitation after stroke is clearly warranted. Pfizer is now conducting a large study for this purpose (http://clinicaltrials.gov/ct2/show/NCT01208233).

Levodopa (l-dopa)

Dopamine's essential role in motor pathways make l-dopa (which is converted to dopamine after crossing the blood-brain barrier) a good candidate as an intervention to influence motor recovery after stroke. However, study paradigms including single-dose and multiple daily dosing have produced mixed results so far.

A randomized, double-blind trial in 53 subjects 6-weeks poststroke found levodopa 100 mg once daily for three weeks was associated with greater motor improvement, which persisted at least three weeks, than placebo.[34] In a placebo-controlled crossover study of ten chronic stroke patients, motor performance was superior in subjects during a five-week course of once-daily levodopa.[35] However, similar studies did not replicate this finding.

Several studies have included the use of **Transcranial Magnetic Stimulation (TMS)** to investigate the physiologic effects of levodopa in chronic stroke patients.[36] TMS can be used to induce certain movements of a muscle group, for example of the thumb. Training and levodopa in some studies influence TMS-induced movements, which suggests that even single-dose levodopa may augment training-induced motor memory,[37] perhaps by modulating motor cortical excitability. Other TMS studies have shown no difference between levodopa and placebo.

Several studies have demonstrated amplification by levodopa of a beneficial effect of speech therapy on verbal fluency and repetition in aphasic patients, particularly in the setting of anterior lesions.[38] Similar studies have had conflicting results, however. Inconsistent results have similarly been found in studies of other medications' effects on aphasia recovery.

Other medications

Piracetam, a derivative of GABA used in some parts of the world for myoclonus and cognitive enhancement (not available in the US) has been shown in several studies to improve aphasia in subacute stroke.[39] Its mechanism of action is unknown but it appears to increase brain glucose utilization and cellular metabolism. A PET study showed increased activity in areas supporting language only in a piracetam-treated group.

The acetylcholinesterase inhibitor donepezil improved aphasia after stroke on a measure of severity but not on a measure of day-to-day communication.[40]

Modafinil, known to improve fatigue in patients with multiple sclerosis, was shown in one study to improve fatigue in patients with brainstem or diencephalic strokes but not cortical strokes.[41]

Mirror Therapy

V. S. Ramachandran and colleagues introduced Mirror Therapy as a method to reduce phantom limb pain due to amputation. Observing that painful phantoms are more likely to be present in individuals whose limbs were paralyzed before amputation, they hypothesized that the brain learned that the limb was paralyzed due to lack of proprioceptive feedback upon attempting to move the limb. This "learned paralysis" persists post-amputation, and pain results from the perception that the limb cannot be repositioned from a posture causing discomfort.[42] A "mirror box" was designed to reduce this "learned paralysis."

A vertical mirror is placed in front of the patient between the intact limb and the stump such that the patient sees in the mirror the reflection of the intact limb where the missing limb should be. The patient then performs movements with "both" hands, receiving visual feedback such that "movement" of the phantom limb is perceived visually, and the patient is able to "move" the phantom out of uncomfortable positions. Studies have shown some success in sustained reduction of phantom limb pain by this method.[43]

Use of mirror therapy has been extended to hemiparesis. Altschuler et al studied the effectiveness of mirror therapy in a crossover design in nine subjects with chronic stroke and hemiparesis.[44] The intervention consisted of 15 minutes of practice twice a day for four weeks with either a mirror or a transparent plastic sheet as a control; the following four weeks subjects were crossed over to the other treatment. Blinded observers rated improvement in more subjects during the mirror-treatment phase than during the control phase, and participants reported greater perception of benefit during the mirror phase. The authors suggested that visual perception of normal movement of the (virtual) affected arm compensates for decreased proprioceptive input from the (actual) affected arm resulting in improved function of the (actual) affected arm. Another proposed mechanism is improvement in premotor cortex recruitment as that area may be important for relating visual information to motor control.[45] It has also been suggested that mirror therapy may reduce learned disuse (the basis of CIMT, see above).[46]

Two randomized controlled trials of the use of mirror therapy for hand function after stroke are of interest. The first enrolled 40 inpatients three to 12 months after a stroke[47] and the intervention consisted of 30 minutes per day of mirror vs. sham therapy, five days per week, for four weeks, while continuing a conventional stroke rehabilitation program. The control group could not see the paretic limb as the nonreflective side of the mirror was used. After four weeks of treatment and at a six-month followup evaluation, the treatment group showed significant and lasting improvements in one measure of motor recovery and one measure of functional recovery, but no significant improvement in a measure of spasticity.

A blinded, randomized trial of home-based mirror therapy in subjects with chronic stroke demonstrated a shift in activation in the cortex of the affected hemisphere on functional MRI in subjects undergoing mirror therapy but not in controls.[48] The authors report this is the first study to suggest an association be-

tween mirror therapy and reorganization of cerebral cortex.

Mirror therapy is a promising technique requiring more study to determine which patients are most likely to benefit and at what period during recovery. As a simple, inexpensive, and patient-driven technique, it will have distinct advantages over other current and putative interventions if large controlled trials demonstrate meaningful effectiveness. In addition to phantom limb pain and poststroke paretic upper limbs, it may be useful in the treatment of patients with complex regional pain syndrome, neglect, and lower limb motor impairment.[49]

Conclusions

Advances in basic neuroscience and technology are driving the development of novel interventions to enhance the natural recovery that occurs after stroke. These interventions range from pharmaceuticals, to elegant and inexpensive techniques such as CIMT and Mirror Therapy, to complex technologies including robotic devices and electrical or magnetic stimulation. Although determining appropriate patient populations and risk:benefit ratios is complex in rehabilitation settings, we have the capability to assess these techniques like never before with improved outcome measures and functional imaging. Neurorehabilitation specialists envision being able to offer stroke survivors a wider variety of therapies at various times during the recovery process that are validated to improve functional outcomes through cortical reorganization and other mechanisms. Exactly which interventions to offer which patients and in what sequence or combination remains to be determined.

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This article discusses off-label uses of medication.

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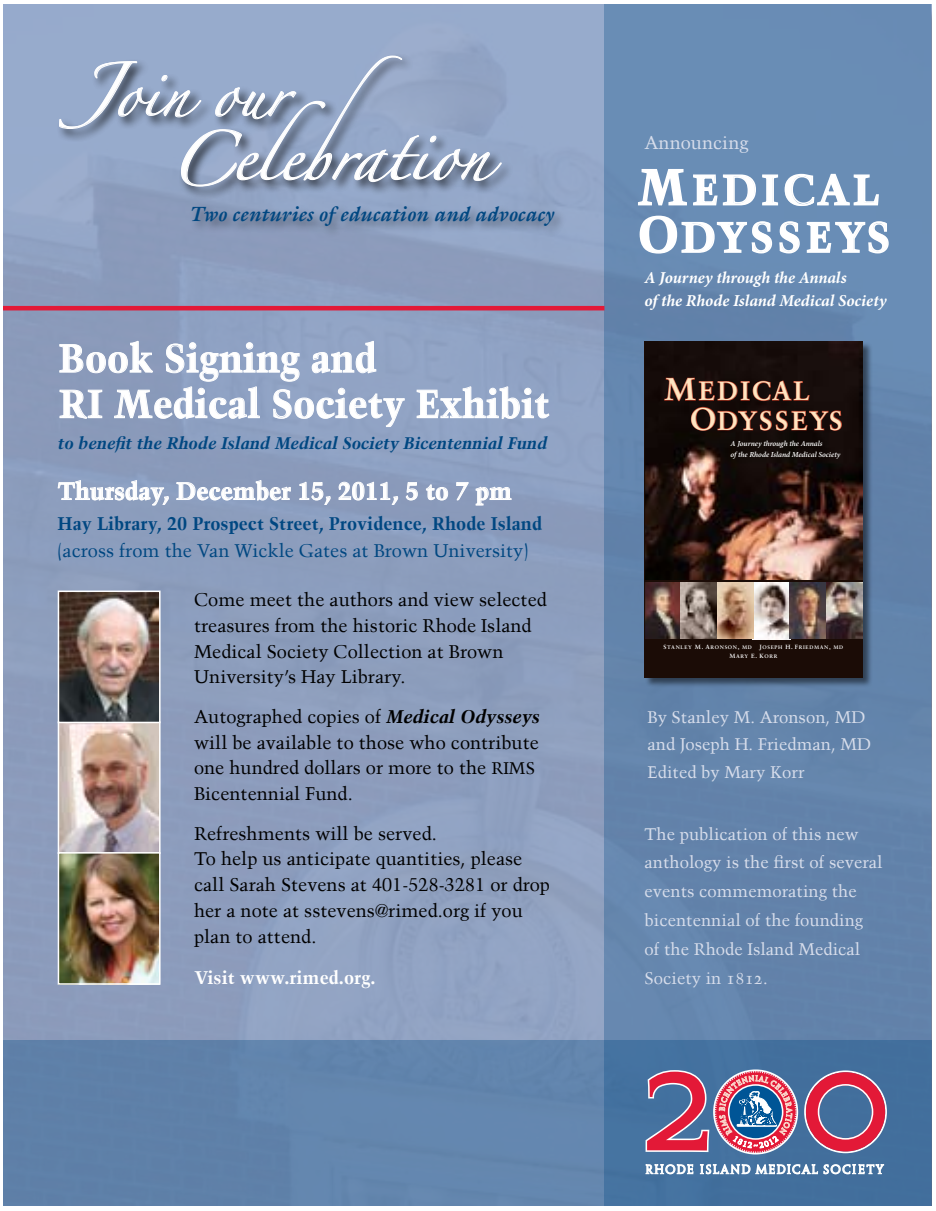
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