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Emerging Treatments for Motor Rehabilitation After Stroke

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Abstract

Although numerous treatments are available to improve cerebral perfusion after acute stroke and prevent recurrent stroke, few rehabilitation treatments have been conclusively shown to improve neurologic recovery. The majority of stroke survivors with motor impairment do not recover to their functional baseline, and there remains a need for novel neurorehabilitation treatments to minimize long-term disability, maximize quality of life, and optimize psychosocial outcomes. In recent years, several novel therapies have emerged to restore motor function after stroke, and additional investigational treatments have also shown promise. Here, we familiarize the neurohospitalist with emerging treatments for poststroke motor rehabilitation. The rehabilitation treatments covered in this review will include selective serotonin reuptake inhibitor medications, constraint-induced movement therapy, noninvasive brain stimulation, mirror therapy, and motor imagery or mental practice.

Keywords

stroke recovery, hemiparesis, physiotherapy, transcranial magnetic stimulation, transcranial direct current stimulation, mental imagery, mirror neurons

Introduction

Stroke is a common health care problem globally, and it is a leading cause of acquired disability worldwide.[1] Unfortunately, the majority of patients with stroke experience incomplete recovery of motor deficits despite intensive rehabilitation, with up to 60% having impaired manual dexterity 6 months following the stroke.[2-4] Stroke-related motor impairments affect independence with functional activities both at home when performing activities of daily living (ADL) and in the community where only a minority of patients with motor impairment are able to return to their professional lives.[3-5] Although there has been an intense focus on acute treatments after stroke, there remains a pressing need for novel treatments and continued research to improve functional motor recovery.

The goal of stroke rehabilitation is to maximize patients' neurologic recovery, functional independence, and quality of life. The multidisciplinary treatment team, including physical therapy, occupational therapy, and speech and language pathology, utilizes a variety of traditional therapeutic interventions to augment spontaneous neurologic and functional recovery following a stroke. However, in recent decades, a number of promising alternative therapies, medications, and experimental treatments have shown benefit to poststroke patients.

In this narrative review, we attempt to familiarize the neurohospitalist with the state of the science in the field of stroke rehabilitation, providing background information and reviewing evidence for several emerging interventions to improve motor recovery following stroke, including selective serotonin receptor inhibitor (SSRI) antidepressants, constraint-induced movement therapy (CIMT), noninvasive brain stimulation (NIBS), mirror therapy (MT), and motor imagery/mental practice. Use of these interventions for nonmotor impairments after stroke will not be reviewed. Of note, although many of the articles cited in this review report distinct outcome measures for motor and functional impairment, the reader is reminded that despite the inherent link between motor impairment and disability, improvement in one does not necessarily indicate improvement in the other.

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Selective Serotonin Reuptake Inhibitor Medications

Fluoxetine, an SSRI developed in 1974,[6] was approved by the Food and Drug Administration in 1987 for use in patients with depression. With the emergence of medications such as fluoxetine which modulate monoamine neurotransmitter activity, research was initiated to define the effects of such medications in different disease states, including stroke. Early animal studies indicated that drugs modulating brain amine concentrations influence the rate and degree of recovery from cortical lesions.[7,8] Subsequently, a number of small trials examined the efficacy of SSRI medications for poststroke depression, emotional lability, and recovery.[9-16] The trials generally demonstrated that SSRI medications were efficacious in treating or preventing poststroke depression, and patients taking SSRI medications after stroke demonstrated few serious side effects. A number of studies on SSRI medications after stroke have also reported outcomes such as neurologic recovery, functional recovery, and independence with daily activities although with mixed results.[10,17,18]

A few small studies have specifically examined the effect of SSRI medications on motor recovery after stroke. In 1 clinical trial, 52 patients with first-time ischemic stroke having hemiplegia were enrolled 1 to 6 months after their stroke and randomized to placebo, maprotiline (a norepinephrine reuptake inhibitor), or fluoxetine for 3 months.[19] The patients randomized to fluoxetine demonstrated significant improvements in gait and greater independence with ADL, as assessed by the Barthel Index (BI), compared to maprotiline, but with no significant outcome difference compared to placebo. Outcomes in the maprotiline group were worse than for the placebo group, but these differences were not statistically significant.

In a double-blind trial of 24 patients with post-stroke depression undergoing acute inpatient rehabilitation, patients were randomized to receive desipramine (n = 13), trazodone (n = 6), or fluoxetine (n = 5) for 4 weeks while also engaging in routine multidisciplinary rehabilitation.[20] After 2 and 4 weeks, patients treated with trazodone or fluoxetine demonstrated statistically significant improvements in functional recovery, as measured by the functional independence measure (FIM), compared to those treated with desipramine. Improvements approached clinically significant change.[21] There were no significant differences between groups in sensorimotor deficits as measured by the Fugl-Meyer Assessment (FMA) or depression as measured by the Hamilton Depression Scale.

In another small prospective, double-blind, crossover, placebo-controlled study, 8 patients with pure motor hemiparesis from a lacunar stroke underwent functional magnetic resonance imaging (fMRI) examinations at 2 and 3 weeks after stroke onset.[22] A single dose of placebo or 20 mg of fluoxetine was given prior to each examination, and motor evaluations of the patient were performed before and during each fMRI. After treatment with fluoxetine, fMRI demonstrated hyperactivation in the ipsilesional primary motor cortex, and patients performed better on motor skill assessments on the affected side.

Based on the results of these and other studies,[18,22-25] a multicenter, randomized, double-blind, placebo-controlled study, the Fluoxetine for Motor Recovery After Acute Ischemic Stroke (FLAME) trial randomized 118 patients with first-time stroke having moderate to severe motor deficits to either fluoxetine 20 mg daily or placebo within 5 to 10 days of symptom onset.[26] Patients with hemorrhagic stroke or moderate to severe depression were excluded from the study. The primary outcome was the Fugl-Meyer Motor Scale score (FMMS), and secondary outcomes included the Montgomery Asberg depression rating scale, National Institutes of Health stroke scale (NIHSS), and modified Rankin Scale (mRS). All patients received routine poststroke rehabilitative therapies. There were no significant differences between groups after 30 days, but patients taking fluoxetine showed statistically significant improvements in FMMS, NIHSS, and mRS compared to placebo at the 90-day assessments. Minimal clinically important differences have not been established for the NIHSS and mRS, but changes did meet clinically important differences cutoff for FMMS.[27] The fluoxetine group also had a significantly lower incidence of depression.

A Cochrane Review published in 2012 evaluating[28] 52 clinical trials found significant benefits of SSRI medications in reducing disability (standard mean difference [SMD] 0.92; 95% confidence interval [CI] 0.62-1.23) and dependency (relative risk [RR] 0.81; 95% CI 0.68-0.97) as well as on neurological deficit (SMD −1.00; 95% CI −1.26 to −0.75), depression, and anxiety.

As usual, risks of treatment should also be considered, and SSRI medications have a number of potential side effects. Of particular note is the small but consistently observed increased risk of bleeding associated with SSRIs. One systematic review and meta-analysis[29] of observational trials calculated that SSRI use was associated with an increased risk of intracranial hemorrhage (adjusted RR 1.51, 95% CI 1.26-1.81) and intracerebral hemorrhage (adjusted RR 1.42, 95% CI 1.23-1.65). Increased risk of bleeding was also noted when SSRIs were taken with anticoagulants. Another study[30] extracted data from a Danish medical registry of patients taking SSRI medications and propensity score matched these patients with nonusers to compute hazard ratios (HRs) of acute myocardial infarction, recurrent stroke, major bleeding, and death, and median follow-up was 1159 days. Use of SSRI was associated with higher risk of overall major bleeding (adjusted HR 1.33; 95% CI 1.14-1.55) and a nonsignificantly higher risk of intracranial bleedings (adjusted HR 1.14; 95% CI 0.62-2.12). Although SSRI use was also associated with lower risk of new cardiovascular events and stroke, overall mortality and mortality due to bleeding event were increased in those taking an SSRI.

Many investigators have explored the effects of SSRI medications on poststroke depression, and more recently, several studies have indicated that administration of these medications in the first several months following stroke may have a beneficial effect on motor recovery and/or reduce disability in patients with poststroke motor impairments. Future studies

Figure 1. Demonstration of constraint-induced movement therapy. During treatment, the patient wears a mitt or constraint on their intact limb, and the impaired limb is used for tasks during therapy and daily activities.

will hopefully confirm these findings and clarify the optimal dosing and duration of treatment. Risks and side effects of treatment with SSRI, including the increased risk of bleeding events, will need to be noted and considered.

Constraint-Induced Movement Therapy

The principles of CIMT originated from the research of Edward Taub on monkeys whose limbs had undergone deafferentation.[31] The underlying concept of CIMT is that restricting the use of the unaffected upper extremity by a mitt or sling will force an individual to use the affected limb to complete task-based activities, affecting neuroplastic change and improving upper extremity function over time.[32] The typical intervention consists of restricting the unaffected limb (Figure 1) for 90% of waking hours for 14 days with 6 hours of therapy for 10 of those days.[33] The inclusion criteria for CIMT include the ability to actively extend the wrist, thumb, and fingers as well as the absence of cognitive impairment, excessive spasticity, or impaired balance. In 1993, Taub et al[32] reported that CIMT resulted in expansion of the cortical motor area responsible for use of the affected limb in patients with stroke and that the treatment also addressed the functional impairment caused by "learned disuse" of the affected limb after stroke.

A number of clinical trials have since explored outcomes among small numbers of patients with stroke treated with CIMT.[34-39] In a larger prospective, single-blind, multicenter clinical trial, the Extremity Constraint Induced Therapy Evaluation (EXCITE) trial,[40] 222 patients were randomized within a mean period of about 6 months from stroke onset to either CIMT or routine care. After a treatment period of 2 weeks, significant improvements were noted in the CIMT group in the quality and speed of arm movements, as measured by the Wolf Motor Function Test (WMFT), and in the quantity and quality of paretic arm use as reported by study patients. At 1-year follow-up, statistically significant differences persisted for all outcome measures except for the WMFT quality of arm movements. The authors also felt that these represented clinically significant differences based on increased functional use of the limb for daily activities reported by patients.

A Cochrane Review of CIMT[41] assessing 19 trials with 619 participants found significant heterogeneity among the trials, including duration of unaffected limb restraint, amount of affected limb exercise, and timing of intervention poststroke. However, 6 studies assessed disability immediately after the intervention, and analysis of data from 184 participants found a modest but statistically significant benefit of CIMT on disability (SMD 0.36, 95% CI 0.06-0.65). Further, a more robust positive effect of CIMT was noted on motor function (SMD 0.72, 95% CI 0.32-1.12), drawing data from 14 studies with 373 participants. The findings were deemed "promising" although concerns remained about the size of the studies, certain methodological weaknesses, the short-term follow-up of patients, and possible publication bias.

Several more recent randomized controlled trials have been subsequently reported. A study randomized 12 patients, average 7 weeks poststroke, to constraint or no constraint for 90% of the day during the study, and all patients received a 3-hour session of therapy daily for 12 days. Improvement was observed in both groups, but no difference was noted between groups in arm and hand motor performance or on self-reported motor ability after 2 weeks of therapy or at 3-month follow-up.[42]

With regard to the use of CIMT in the acute to subacute phase after stroke, there have been only 2 studies in this population to date. One study in 2007 enrolled 23 patients within 14 days of stroke and randomized them to CIMT or equally intensive traditional therapy interventions (3 hours/d, 6 days/wk for 14-15 days).[43] However, no statistically significant differences were noted between groups immediately after treatment or after 3 months based on the Fugl-Meyer upper extremity motor scores.

A larger single-blind, randomized controlled trial was published in 2009, known as the Very Early Constraint-Induced Movement during Stroke Rehabilitation (VECTORS) trial.[44] Fifty-two patients were enrolled, all undergoing acute rehabilitation with first-time ischemic or hemorrhagic stroke and upper extremity weakness. Each was randomized to 1 of the following 3 dose-matched treatment arms: traditional upper extremity therapy, standard intensity CIMT, or high-intensity CIMT. Standard intensity CIMT included 2 hours/d of therapy, and patients wore the constraint 60% of the day. High-intensity

CIMT included 3 hours/d of CIMT treatment, and the constraint was worn for 90% of the day. This study also found no difference in upper extremity function between traditional therapy and standard CIMT as measured by the Action Research Arm Test (ARAT). Interestingly, the high-intensity CIMT group demonstrated significantly lower ARAT scores than the other 2 groups.

A more recent meta-analysis of CIMT evaluating 14 studies and 479 patients with acute and chronic stroke found a small but significant effect of CIMT on motor function (SMD 0.44, 95% CI 0.03-0.93), although no significant effect on disability.[45] The authors note the uncertainty that remains regarding the magnitude of the effect of CIMT as well as whether or not the motor improvements achieved with CIMT are likely to translate into any functional improvement for patients.

Another meta-analysis explored the effect of CIMT on patients greater than 6 months after stroke.[46] The meta-analysis included 572 patients in 16 studies, each of which met the criteria of having at least 50% of patients with stroke, a randomized controlled study design, a CIMT intervention, and a standard therapy control group. Patients treated with CIMT were noted to have improved control of hand and arm placement as well as improved strength compared to standard therapy treatments, but the speed of task performance was unchanged.

Although a significant body of literature generally supports the use of CIMT in the subacute and chronic poststroke populations, several limitations of CIMT remain. With regard to acuity, CIMT has not demonstrated superiority to routine acute rehabilitation interventions, and as noted previously, high-intensity therapy may even have a detrimental effect on recovery. Additionally, the intervention is tiring to the patient and labor intensive on the part of the therapist, requiring treatment for up to 5 to 8 hours/d, limiting the clinical utility of CIMT. In a survey of 208 patients with stroke, 68% were not interested in participating in CIMT mainly due to the intensity of the therapy and 68% of therapists felt that administration of CIMT would be "difficult" or "very difficult."[47]

The difficulties in both providing and tolerating CIMT led to the development of a modified CIMT protocol[48] with reduced formal session duration (1/2 hour, 3 days/wk) and less time with the constraint in place (5 hours/d, 5 days/wk) although with a more prolonged treatment course of 10 weeks. A study of 35 patients with chronic stroke comparing the modified CIMT protocol to a time-matched exercise program or to no therapy found significantly greater improvements in the ARAT and Motor Activity Log Amount of Use and Quality of Movement subscales among those in the modified CIMT group compared to the other groups.[49]

A telerehabilitation approach has also been described[50] in order to address issues with access and administration of the therapy. In a study of 7 patients, a device was utilized that automates the upper limb training component of CIMT, and effectiveness of this training was assessed in a telerehabilitation setting with remote supervision and only intermittent interaction with a therapist. Patients received 3 hours of therapy with the device for 10 consecutive weekdays. Gains on the WMFT and the Jebsen-Taylor Hand Function Test were statistically significant ($P < 0.05$, $d' > 0.9$). Changes in WMFT did not meet cutoffs for minimal clinically important change.[51]

Another limitation of CIMT is the exclusion of patients who cannot demonstrate active extension of the wrist, thumb, and fingers, and limited motor function excludes 4 of 5 otherwise eligible patients with stroke from participation in a CIMT program.[52] Such exclusion criteria limit the utility of CIMT to a fraction of the overall stroke population with persistent motor dysfunction. Furthermore, the generalizability of the reported benefits of CIMT to patients with more severe motor weakness and greater functional impairments remains uncertain. Studies combining other treatments such as EMG-triggered stimulation with CIMT have attempted to bridge the period of poor motor performance although with unclear results.[53,54]

In summary, studies evaluating the effects of CIMT on upper extremity recovery in poststroke patients have demonstrated significant improvements in motor and functional outcomes, although there have been mixed results. The motor and functional benefits appear to occur in poststroke patients who, at baseline, have active wrist and finger extension, good cognition, limited spasticity, and preserved balance. However, significant barriers may prevent widespread integration of CIMT with current poststroke rehabilitation treatments.

Noninvasive Brain Stimulation

Noninvasive brain stimulation involves the application of weak electric or magnetic fields to the brain via the surface of the scalp with the goal of changing or normalizing brain activity.[55-58] Noninvasive brain stimulation has been predominantly utilized in the study of brain physiology and function, neuroplasticity and its behavior relevance, and the functional networks between various brain regions.[59-62] However, an accumulating body of evidence supports a therapeutic potential in stroke rehabilitation and a variety of other neurological conditions.[63-66] Noninvasive brain stimulation is particularly appealing to clinicians and neuroscientists as it modulates brain excitability and functional plasticity with relative safety and facilitates motor learning when combined with a motor task.[67,68] Available NIBS techniques continue to expand, but the 2 most common forms are transcranial magnetic stimulation (TMS; Figure 2A) and transcranial direct current stimulation (tDCS; Figure 2B). Neither modality is FDA approved in stroke rehabilitation, but both are currently being studied under off-label research purposes. Transcranial magnetic stimulation uses a rapidly changing magnetic field to induce electric currents in the brain, causing neuronal depolarization and action potentials. Transcranial direct current stimulation uses a small battery-powered device to deliver weak electric currents (usually 1-2 mA) to the brain via saline-soaked sponges placed over the stimulation site.

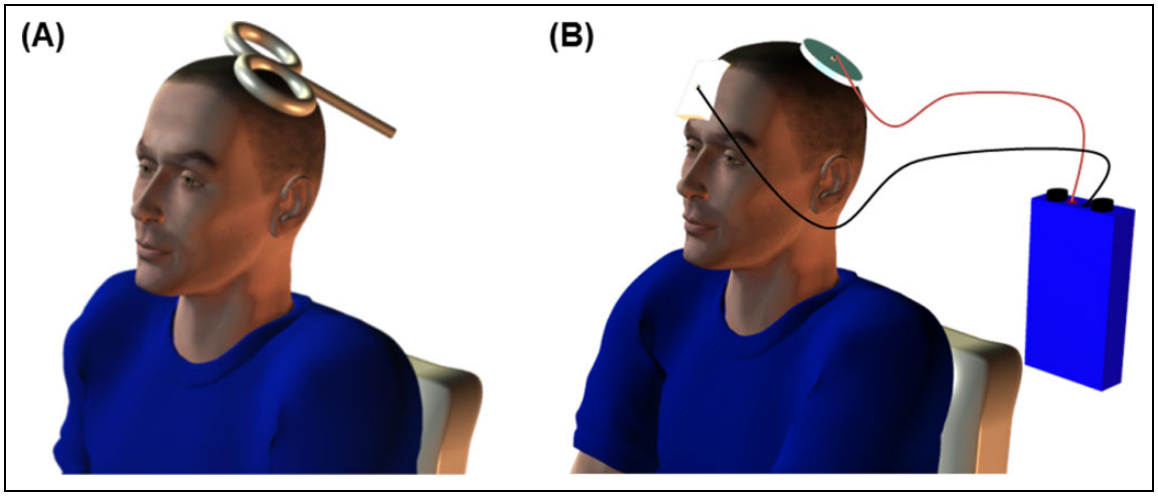

Figure 2. Schematic representation of noninvasive brain stimulation techniques. A, Transcranial magnetic stimulation (TMS) of the brain using a figure-of-8 coil. B, Transcranial direct current stimulation (tDCS) of the brain with the active electrode (red wire, anode) placed over the primary motor cortex and the reference electrode (black wire, cathode) placed over the contralateral supraorbital region.

The overarching aim of these brain stimulation techniques in stroke rehabilitation is to modify cortical activity and neuroplasticity through an increase in ipsilesional cortical excitability and/or a decrease in contralesional cortical excitability (Figure 3).[63,69,70] Depending on the technique used, the direction of neuromodulatory effects (ie, increase or decrease in cortical excitability) is achieved by altering the frequency at which the stimulation is performed, changing the pattern of stimulation or reversing the polarity of the electrodes.[63] In recent years, the feasibility and effectiveness of NIBS in modulating cortical excitability and in facilitating motor recovery after stroke has been studied. Both TMS and tDCS are not only safe and effective in modulating cortical excitability but have also shown to enhance motor adaptation and learning and influence motor memory consolidation in both healthy adults and stroke survivors.[67] Importantly, the modulation of cortical excitability often parallels clinical improvement in motor performance and outcome among stroke survivors.[71-73]

The dosage of the applied stimulation in NIBS is a key factor in determining the extent of neuromodulation and associated functional or behavioral plasticity. Typically, stronger stimulation intensity or a longer duration of stimulation will lead to a greater neuromodulatory effect. However, increased stimulus dosage appears to also increase the potential risk of adverse events, including seizure, headache, and muscle twitching. Accordingly, safety guidelines have been established for the application of TMS and tDCS in research and clinical settings.[25,74,75] Both techniques are considered safe with rare incidence of adverse events when safety guidelines established for these procedures are followed. Therefore, appropriate training and familiarity with the safety, ethical, and application guidelines of TMS/tDCS among clinicians and researchers is necessary before the use of these techniques.

Studies have explored the efficacy of NIBS for improving motor recovery after stroke but results of meta-analyses on the

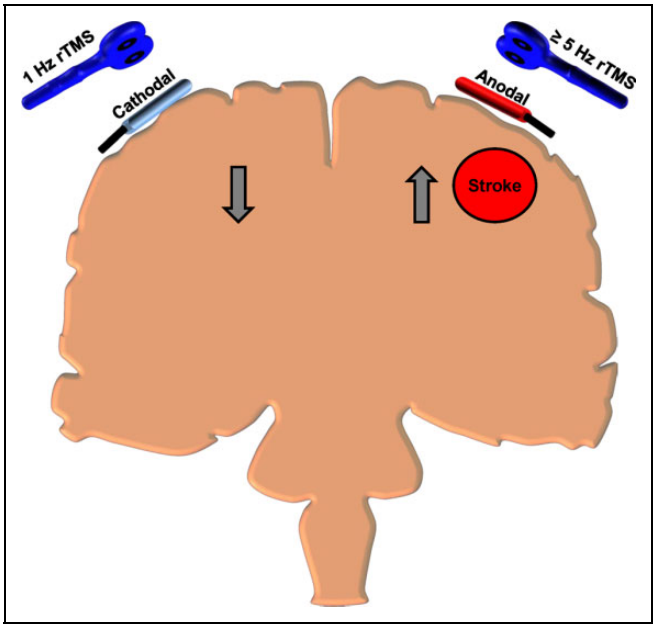

Figure 3. Schematic representation of noninvasive brain stimulation techniques for facilitating motor recovery after stroke. The overarching aim of these techniques is to upregulate (↑) cortical excitability of the lesioned hemisphere or to downregulate (↓) cortical excitability of the contralateral nonlesioned hemisphere. The rationale for inhibiting cortical excitability of the nonlesioned hemisphere is that it is expected to minimize the amount of interhemispheric inhibition from the nonlesioned hemisphere to the lesioned hemisphere while performing active movements of the paretic limb. Note that cortical excitability can be facilitated by applying anodal tDCS or high-frequency rTMS and can be diminished by applying cathodal tDCS or low-frequency rTMS. Red-filled circle labeled with stroke indicates lesioned hemisphere. tDCS indicates transcranial direct current stimulation; rTMS, repetitive transcranial magnetic stimulation.

benefits of treatment have been mixed. A meta-analysis of 50 randomized clinical trials and 1282 patients with stroke found that both TMS and tDCS were effective in improving motor outcomes after stroke,[76] although substantial heterogeneity between trials was noted. A Cochrane Review of 19 trials involving 588 stroke survivors did not find a beneficial effect of rTMS for the treatment of motor dysfunction after stroke.[77] Another meta-analysis of 8 randomized placebo-controlled trials examined the isolated effects of anodal tDCS in the treatment of motor dysfunction after stroke,[78] and a pooled analysis found a small but significant improvement in functional outcome of patients with stroke having chronic deficits after anodal tDCS compared to baseline measurements (SMD 0.40; 95% CI 0.10-0.70, $P = .01$) and sham stimulation (SMD 0.49; 95% CI 0.18-0.81, $P = .005$).

Although more studies have evaluated the effects of NIBS on upper extremity motor recovery and functional improvements after stroke, a few studies have also examined the potential role of NIBS in improving gait following stroke.[79-81] One study examined the effects of 1-Hz rTMS over the leg motor area of the unaffected hemisphere followed by task-oriented functional training on walking performance in 24 chronic stroke survivors.[80] Ten sessions of 1-Hz rTMS combined with task-oriented training induced significant improvements in various gait parameters when compared to sham stimulation and task-oriented training. Another study evaluating the combined effects of anodal tDCS and robotic training on gait function among chronic stroke survivors with low ambulatory capacity found improved outcomes in those receiving active tDCS compared to the sham stimulation.[81] Collectively, the available evidence suggests that NIBS combined with mobility and gait training may be a safe and feasible approach to improving walking function in stroke survivors.

Although the results from several small-scale clinical trials appear promising and encouraging, the role of NIBS in stroke rehabilitation remains unclear for a variety of reasons. First, there is a dearth of large-scale clinical studies with adequate long-term follow-up of patients with stroke. Second, the observed improvements are of modest clinical significance with questionable effect size. Third, the optimal way of combining NIBS with physical rehabilitation (ie, whether TMS or tDCS should precede, follow, or be combined with therapy) is still unclear. The uncertainty about the timing of NIBS is critical because the homeostatic metaplastic mechanisms (ie, mechanisms that stabilize and regulate plasticity within a physiological range) following NIBS and active behavioral intervention may limit its neuroplastic effects.[82,83] Finally, TMS- or tDCS-induced directional modulation of motor cortical excitability is known to be variable both within and between patients,[84,85] limiting the applicability among all patients with stroke and necessitating a careful selection of patients for therapy. Although the picture is far from clear, ongoing investigations will hopefully address these limitations and further define the role of NIBS in stroke rehabilitation.

Figure 4. Demonstration of mirror therapy. The patient places their intact limb and head on the same side of the mirror, outside the mirror box. The impaired limb is placed in the mirror box out of view by the patient while the patient executes movements with the intact limb or both limbs.

Mirror Therapy

Vilayanur S. Ramachandran first reported the use of a mirror for the treatment of postamputation phantom limb pain in 1995.[86] Treatment with MT involves the placement of a mirror in the mid-sagittal plane, allowing the patient to perceive the reflection of the intact limb as if it were the affected one (Figure 4). Ramachandran and colleagues theorized that the illusory perceptions of the limb would counteract maladaptive neuroplastic changes that may occur in the absence of sensory afferents.[87] Neuroplastic changes also occur in the brain following stroke, and MT has been examined as a potential therapeutic modality for patients with stroke as well.[88] The first study utilizing MT after stroke examined 9 patients with chronic stroke who were randomly assigned to use either a mirror or a transparent plastic for the exercises for 4 weeks with each group then crossing over to the other treatment for the remaining 4 weeks.[89] In this small study, the progress from baseline in upper extremity movement ability of patients using MT was noted in range of motion, speed, and accuracy. Two subsequent case reports also noted positive effects of MT on upper extremity movement after stroke.[90,91]

Another study of 40 patients with hemiparetic, first-time stroke investigated MT for recovery of lower extremity function.[92] Patients were excluded if they were greater than 1-year poststroke, at a later stage of motor recovery after stroke (Brunnstrom stroke stage >3) or demonstrated significant cognitive impairments. Patients were randomized to receive either 20 sessions of MT (30 minutes each) or 20 sessions of a sham treatment in which they flexed their intact ankle

without reflection. The MT group demonstrated significant improvements compared to the control group for motor recovery and motor functioning at 6-month follow-up based on FIM measurements. These FIM changes do meet cutoffs for clinically important differences.[21]

In a study evaluating whether MT could be effectively utilized in the home environment, 40 patients with chronic stroke were randomized for 6 weeks to either a control group, which performed bimanual tasks, or a MT group, which executed tasks with the affected limb obscured.[93] All patients received 1 session of supervised therapy per week with instructions to perform 5 additional 1-hour sessions at home per week. The MT group demonstrated significant improvement in motor function at the completion of the treatment period but had no significant improvement at 6-month follow-up.

The effect of MT on patients less than 6 months from first-time stroke has also been studied.[94] In this study, 26 patients with stroke were randomized to routine rehabilitation or routine rehabilitation plus two 25-minute sessions of MT for 5 days per week over a period of 4 weeks. Significant improvements in upper limb motor recovery and motor functioning, as measured by the FMA and Brunnstrom stage of motor recovery, were noted immediately following treatment although longer follow-up was not reported.

In 2012, a Cochrane Review of 14 studies including 567 patients with stroke found a positive effect of MT on motor function (SMD 0.61; 95% CI 0.22-1.0; $P = 0.002$) and ADL (SMD 0.33; 95% CI 0.05-0.60; $P = 0.02$).[95] However, the results of the review were limited by small sample sizes of most included studies, heterogeneous control interventions, and methodological limitations of some studies.

Several additional randomized, controlled trials of MT on upper extremity function after stroke have been reported over the past few years. One study noted improvements in FMA scores and kinematic measures of reaching,[96] while another study reported improvements in ARAT and FIM scores.[97] Finally, in a study of 60 patients with severe arm paresis following stroke, subjects were randomized into groups receiving control therapy with the limb obscured, individual MT, or group MT.[98] Stroke outcomes were assessed by the FMA, ARAT, BI, the Stroke Impact Scale, and the Star Cancellation Test. After 5 weeks, no significant difference between groups was observed in motor function, ADL, or quality of life.

Studies evaluating the benefits of adding MT to routine stroke rehabilitation have generally demonstrated statistically significant improvements in motor and functional outcomes although interpretation of these studies is limited by high methodologic heterogeneity and small sample sizes. Future studies will hopefully clarify the optimal timing, dose, frequency, and duration of MT as well as which patient populations respond best to treatment. A multicenter clinical trial is underway,[99] which may provide more conclusive evidence of a beneficial effect of MT.

Motor Imagery/Mental Practice

Studies in the first half of the last century suggested that mental rehearsal of motor tasks resulted in improved performance on simple motor tests.[100] Termed "mental practice," this mental rehearsal of movement was initially studied in the field of sports psychology.[101] Mental practice with motor imagery was felt to induce cortical activity, leading to the investigation of a therapeutic use in post-stroke patients. With regard to terminology, "motor imagery" is considered the mental execution of a skilled movement without actually performing the movement, whereas "mental practice" (MP) describes a training or therapy task in which an internal representation of the movement is activated and the execution of the movement repeatedly mentally simulated, without physical activity.

Physiologically, motor imagery appears to activate many of the same areas involved in the execution of motor tasks,[102] and multiple imaging studies utilizing PET and fMRI scans have detailed overlap in cortical activation patterns between actual movements and imagined motor activation.[103,104] Overlapping areas of activation vary by study but appear to consistently include the premotor cortex, supplementary motor area, superior parietal or somatosensory cortex, and inferior parietal cortex.[105] The overlap of multiple cortical areas likely reflects activity within the proposed mirror neuron system: a frontoparietal neural network active during times of motor learning, including performing, imagining, or observing an action.[106]

A number of clinical trials among patients with stroke having motor impairments have assessed the effects of MP on upper extremity motor recovery, independence with ADL, balance, and gait.[107-115] Heterogeneous methodologies have been employed in the studies evaluating the effect of MP on upper extremity function, especially in how the treatment is administered, the treatment duration and frequency, the type of control group intervention, and the follow-up duration.[109,112-116] Variations in the studies also include inconsistent methodology with regard to randomization, blinding, and assessment of compliance. Nevertheless, most of the studies found a positive effect in patients treated with MP, although 2 studies have failed to show a benefit, including a study of poststroke nursing home patients[116] and a randomized trial of patients with a residual upper limb weakness within 6 months following stroke.[112] In a recent randomized, single-blinded study of 32 chronic stroke survivors with hemiparesis (mean of 3.6 years following first stroke),[114] patients engaged in either 30 minutes of MP or relaxation twice weekly for 6 weeks while also receiving routine therapy. The primary outcome measures were the FMA and ARAT at the end of the treatment period. The MP group demonstrated statistically significant reduction in affected arm impairment and a significant increase in daily arm function. Improvements in ARAT met cutoff for clinically important difference,[117] but changes in FMA did not.[27]

A Cochrane Review of 6 studies involving 119 stroke survivors found that MP in combination with rehabilitation treatment is more effective in restoring arm function of stroke survivors in comparison to the rehabilitation treatment alone (SMD 1.37; 95% CI 0.6-2.15; $P = 0.0005$).[118] Currently, there have been no large studies of MP, although a multicenter randomized controlled trial to evaluate the clinical effectiveness of MP with motor imagery is underway.[119]

Even if MP treatments are beneficial beyond standard therapy interventions, the characteristics of an ideal treatment protocol remain unclear. Given the potential for functional cerebral reorganization with MP, an effective protocol would likely require sustained attention, appropriate visualizations, and sustained treatment. Further studies are needed to clarify optimal MP duration and methodology, timing of the intervention, and required number of treatments. Future research will also need to elucidate the characteristics of patients that respond best to MP therapy.

Regardless of the potential limitations of MP, the ease of implementation, ability to perform the treatments outside of the clinic, and low cost are all attractive attributes of this unique treatment. Mental practice may represent a useful adjunct to current treatments if sufficient evidence supports its application.

Conclusion

In order to familiarize the neurohospitalist with the state of the science supporting emerging poststroke motor rehabilitative treatments, this review summarizes the history and current evidence supporting the use of SSRI medications, CIMT, NIBS, MT, and mental practice. Each of these interventions seeks to augment spontaneous neurologic recovery or modulate neuroplastic change following stroke. Given the emerging evidence in support of improved outcomes and the potential clinical implications of these treatments, active research within these fields is progressing rapidly.

Despite the recent meta-analyses providing greater insight into the efficacy and effect size of these emerging treatments, there is a clear need for randomized trials adequately powered to address numerous uncertainties. Ongoing research will need to examine the optimal treatment dose, timing of intervention, duration of intervention, and ideal patient population. Nonetheless, there is active interest and discussion regarding how these interventions might be integrated with current therapies.[120-122]

With high-quality studies ongoing for many of these treatments, they may gain more widespread acceptance. If so, the stage may be set for a new standard of care and significant advancement within the field of stroke rehabilitation.

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