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Noninvasive Brain Stimulation in Stroke Rehabilitation

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Summary: Stroke is a common disorder that produces a major burden to society, largely through long-lasting motor disability in survivors. Recent studies have broadened our understanding of the processes underlying recovery of motor function after stroke. Bilateral motor regions of the brain experience substantial reorganization after stroke, including changes in the strength of interhemispheric inhibitory interactions. Our understanding of the extent to which different forms of reorganization contribute to behavioral gains in the rehabilitative process, although still limited, has led to the formulation of novel interventional strategies to regain motor function. Transcranial magnetic (TMS) and DC (tDCS) electrical stimulation are noninvasive brain stimulation techniques that modulate cortical excitability in both healthy individuals and stroke patients. These techniques can enhance the effect of training on performance of various motor tasks, including those that mimic activities of daily living. This review looks at the effects of TMS and tDCS on motor cortical function and motor performance in healthy volunteers and in patients with stroke. Both techniques can either enhance or suppress cortical excitability, and may move to the clinical arena as strategies to enhance the beneficial effects of customarily used neurorehabilitative treatments after stroke. **Key Words:** Stroke, motor cortex, rehabilitation, cortical stimulation, transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), plasticity.

INTRODUCTION

An estimated 700,000 Americans suffered a stroke during 2005, incurring estimated costs related to their care of approximately $56.8 billion.[1] Stroke is a leading cause of serious long-term disability, and approximately 1.1 million Americans with stroke had functional limitations in activities of daily living in 1999.[2] The burden of stroke-related disability is predicted to increase in the coming decades in proportion to the expansion of the elderly population.[3] Stroke case-fatality has declined, but stroke incidence has not, leading to rising numbers of stroke survivors.

After ischemic damage to motor areas of the brain, patients experience some degree of spontaneous recovery,[4,5] increasingly so since the advent of interventions implemented in the acute period after stroke—notably, use of tissue plasminogen activator (TPA) to dissolve blood clots. TPA represents an important advance in the fight against this disease, but so far has benefited a limited proportion of stroke patients.[6] More than 50% of stroke survivors who reach the chronic stage experience permanent motor deficits.[7] Repetitive task-oriented motor training represents the current standard in neurorehabilitation after chronic stroke.[8,9] In recent years, new strategies in repetitive motor training have raised substantial interest, including constraint-induced therapy,[10–12] bilateral arm training,[13,14] body-weight support treadmill training,[15–17] robotic assisted therapy,[18–24] and use of virtual reality protocols.[25–30]

MECHANISMS OF FUNCTIONAL RECOVERY

Studies of cortical plasticity after stroke suggest that the damaged cortex has the potential for extensive reorganization (for a review, see Ward and Cohen[31] and Calautti and Baron[32]). Among possible mechanisms of neural plasticity contributing to functional recovery are dendritic sprouting over time,[33,34] new synapse formation,[35] and long-term potentiation (LTP) and depression (LTD).[36,37] Reorganization after stroke may also involve undamaged areas of cortex taking on functions of the infarcted regions.[38] Different forms of reorganization that may contribute to functional recovery include diaschisis, peri-infarct reorganization, activity in the ipsile-

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sional or in the contralesional hemisphere, interhemispheric interactions, and vicarious reorganization.

Diaschisis

In diaschisis, there is functional deactivation of undamaged areas of the CNS that are remote but connected to the lesioned area.[39] Imaging studies in stroke patients have shown diaschisis in cerebellar structures in the motor domain[40–44] and also in other regions related to language[45] and vision[46] processing. Resolution of cerebellar diaschisis has been proposed as one of the mechanisms contributing to recovery of motor function after stroke;[47,48] for example, after intake of amphetamines.[49,50]

Peri-infarct reorganization

Peri-infarct reorganization can occur after focal cortical lesions in the primary motor cortex.[51,52] This form of plasticity, described in nonhuman primates, may contribute to motor recovery by allowing other areas near the lesioned area to gain control of the weak body part.[51,52] In humans, Jaillard et al.[53] for 2 years followed a group of four stroke patients who had a small lesion located in the primary motor cortex (M1) and found that recovery of finger movements was associated with a dorsal shift of the cortical activation areas within M1. Note, however, that such focal cortical lesions restricted to M1 are not commonly seen in stroke patients. Additionally, in human studies the increased magnitude of peri-infarct activation seen under functional MRI (fMRI)[54] does not show a direct correlation with the magnitude of motor recovery,[55] raising the question of the degree to which peri-infarct reorganization contributes directly to motor recovery. Such findings underscore both the importance of designing realistic animal models of human stroke, and its complexity.

Activity in the ipsilesional hemisphere

In addition to the peri-infarct rim, increasing levels of activation have been reported in a distributed ipsilesional network that includes primary motor cortex, premotor cortex, supplementary motor area, and bilateral Brodmann area 40 in stroke. These findings correlated positively with one index of motor recovery, the hand score of the motricity index.[56] Taken together, these neuroimaging studies suggest that activation in ipsilesional motor areas plays an important role in the recovery process. Neurophysiological studies showed that transient disruption of activity in the ipsilesional M1 and dorsal premotor cortex of patients with chronic stroke and good motor recovery caused clear transient deficits in motor performance of the paretic hand.[57,58] Altogether, these findings suggest that motor performance in the paretic hand of patients with good motor recovery relies predominantly on reorganized activity within the lesioned hemisphere.[31]

Activity in the contralesional hemisphere

The unaffected hemisphere is another important locus of reorganization after stroke. Increased levels of contralesional sensorimotor activation have been identified during simple movements of the paretic hand.[59,60] The magnitude of contralesional activation appears to decrease in M1 at 3 to 6 months, relative to 1 week after the stroke,[60,32] but the intensity of contralesional M1 activity does not correlate with the degree of recovery.[56] This finding might indicate that contralesional activation is not functionally relevant for recovery,[56] or that it is insufficient to compensate for a marked motor deficit.

Increased contralesional activation may be most prominent in the early stages after stroke, and with later refocusing of activation back to the ipsilesional motor regions.[61] Consistent with this view, disruption of activity in contralesional M1 did not greatly disrupt paretic hand function in patients with chronic subcortical stroke and good motor recovery.[57] On the other hand, disruption of activity in the contralesional dorsal premotor cortex resulted in disruption of a reaction-time task in patients with poorer recovery.[62] Moreover, higher levels of contralesional activity in secondary motor areas (prefrontal and parietal cortices) appear to be predictive of a slower motor recovery, suggesting a possible role for activity in the intact hemisphere in patients with lesser or unsuccessful recovery.[56] A recent study, however, applied fMRI-guided TMS overactivated areas of the contralesional hemisphere and found that a complex behavioral task could be disrupted in chronic subcortical stroke patients but not in a healthy age-matched group.[63]

Regardless of the specific role of each hemisphere, it is clear that recovery processes are likely to rely on the operation of more extensive ensembles of neurons organized in neural networks that link activity in different cortical sites of both hemispheres. Additionally, the role that activity in the intact and affected hemispheres plays in motor control is likely to vary, depending on lesion sites, time from stroke, complexity of the behavioral task, and magnitude of impairment.[31,63,64] If this is the case, caution is advised in drawing definite conclusions about the involvement of different ipsi- and contralesional regions in the process of functional recovery.

Interhemispheric interactions

Interactions between the hemispheres can also contribute to reorganization. One example is interhemispheric inhibition between homonymous motor cortical representations.[65] Transcallosal fibers are known to transmit inhibitory influences between the homologous areas of both hemispheres.[66] These fibers are thought to be glutamatergic and to project onto inhibitory GABAergic interneurons.[67] Patients with stroke have changes in motor cortical excitability[68–70] and an abnormally high interhemispheric inhibition from the contralesional M1 to the ipsilesional M1 with movements of the paretic hand.

These changes are observed in association with movements of the paretic hand, but less so or not at all at rest. The increased interhemispheric inhibition is more prominent in cases with more substantial motor impairment,[65] a finding consistent with previous work on interhemispheric competition in sensory areas. These findings led to the proposal of a similar model in the motor domain (see Ward and Cohen[31]). Under this model, purposeful modulation of excitability in motor regions of the intact and affected hemisphere using noninvasive brain stimulation could potentially contribute to functional restoration.[71]

Vicarious reorganization

In vicarious reorganization, a healthy region of the brain could take over the function of another, lesioned brain area. The term has been used to explain the finding of functional recovery after certain brain lesions.[72] Evidence for this type of process exists in animal models[51,73,74] and in humans.[53]

NONINVASIVE BRAIN STIMULATION

Recent work has raised the possibility that brain stimulation can enhance the beneficial effects of motor training in the rehabilitative process.[31] Studies in animal models showed that motor recovery after focal lesions in the primary motor cortex can improve with direct epidural cortical stimulation.[75,76] Human studies addressing this possibility are currently underway.[75] In parallel with these invasive approaches, there has been increasing interest in testing the effects of noninvasive cortical stimulation in the rehabilitative process. Transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) have been investigated as potential tools for modulating motor recovery in stroke or influencing motor, sensory, and cognitive functions.

TMS is delivered by passing a strong brief electrical current through an insulated coil placed on the skull. The current induces a transient magnetic field in the brain, and electric currents in the cortex flow parallel to the coil, thereby depolarizing neurons. TMS can enhance or decrease activity in cortical regions and influence function, depending on multiple variables such as the frequency, duration of stimulation, the shape of the coil, and the strength of the magnetic field. The effects of repetitive TMS (rTMS) on cortical excitability can outlast the stimulation period for as much as 1 to 2 hours.[77,78]

tDCS at intensities of 1 to 2 mA is applied through two surface electrodes placed on the skull. Depending on the duration and the polarity of the stimulation, tDCS can increase or depress excitability in the stimulated region from minutes to 1 to 2 hours. tDCS does not appear to induce direct neuronal depolarization, as does TMS; instead, it modulates the activation of sodium- and calcium-dependent channels and NMDA receptor activity, promoting LTP- and LTD-like changes.[79–81]

The duration of effects elicited by a single application of either TMS or tDCS appears to be comparable (up to hours). Both techniques are noninvasive and appear to be safe when used within established safety guidelines. The mechanisms underlying their effects, however, may differ. TMS equipment is more expensive, but can stimulate more focally and exhibits a better time resolution (TMS can be applied with millisecond accuracy, but tDCS requires several minutes). There is more experience in the use of TMS protocols than of tDCS, but for double-blind experimental designs sham tDCS is easier to achieve than sham TMS.[82] In rehabilitative settings, tDCS is more easily applied simultaneously with cognitive or motor training protocols. Thus, the choice of technique depends largely on the particular hypothesis to be tested and the experimental setting.

In terms of safety, the main issue raised with rTMS has been the possibility of seizures; however, available rules of application and training protocols have made them a rare event.[83] Individuals with history of seizures are largely excluded from rTMS studies (except in trials geared to test the possibility of beneficial effects in some forms of epilepsy). For tDCS, on the other hand, there are no reports of seizures, but safety studies are still required. tDCS often elicits short-lasting tingling sensations at the beginning and end of the stimulation period, rarely accompanied by redness under the electrode sites.[81,82,84] Occasional transient headaches have been described for both TMS and tDCS. Both rTMS and tDCS appear to be safe if used within proposed safety limits.

Additional points to keep in mind are that: (1) application of TMS or tDCS to one cortical site will probably influence distant cortical or subcortical sites through trans-synaptic effects[85,86]; (2) in patients with brain lesions, expected models of current flow elicited by rTMS or tDCS may differ from those in healthy volunteers[87]; and (3) both techniques may potentially influence attention, fatigue, discomfort, or mood, which underscores the importance of controlling for these factors in the design of double-blind clinical trials.

Recent work has documented beneficial effects of noninvasive brain stimulation on cognitive functions in healthy humans and nonhuman primates. High-frequency rTMS applied to the primary motor cortex resulted in performance improvements in reaction-time tasks[88] and in motor sequence learning.[89] Consistent with these data, application to primary somatosensory cortex produced lasting improvements in two-point tactile discrimination and an enlargement of the right index finger representation in S1, as measured by fMRI.[90]

Similar findings have been reported with tDCS. Early

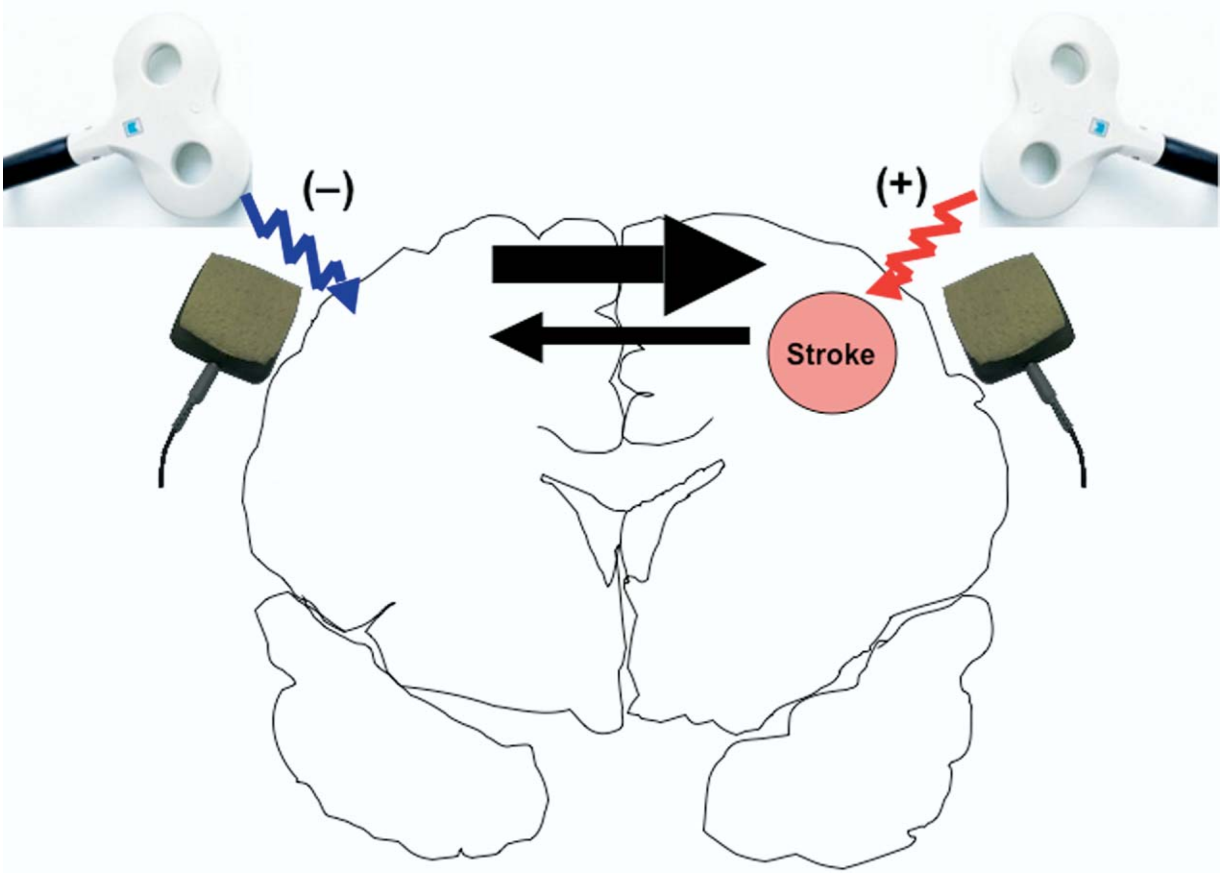

FIG. 1. Possible therapeutic uses of noninvasive brain stimulation to promote recovery in chronic stroke (in this diagram, transcranial magnetic stimulation [TMS] and transcranial direct current stimulation [tDCS]). Cortical reorganization after stroke produces an imbalance of interhemispheric inhibition, which may be reduced by inhibitory TMS or transcranial direct current stimulation (tDCS) to the contralesional hemisphere. Alternatively, beneficial forms of reorganization may be promoted by excitatory TMS or tDCS to the ipsilesional hemisphere.

studies in nonhuman primates demonstrated that anodal tDCS to dorsolateral prefrontal (DLPF) cortex could improve learning of a simple motor reaction time task.[91] In humans,[92,93] application of anodal tDCS has been reported to improve implicit learning when applied to the primary motor cortex[94] and to enhance working memory and probabilistic classification learning when applied to the DLPF cortex.[95,96] Visuomotor learning was facilitated with anodal tDCS applied to the primary motor cortex or to area V5 of occipital cortex.[97]

The mechanisms underlying these effects are incompletely understood, but they could include modulation of LTP- or LTD-like processes,[98] as well as nonspecific changes such as generalized postsynaptic excitability enhancements.[99] These well documented effects of noninvasive brain stimulation in healthy subjects support possible application in stroke patients.

Models of interhemispheric competition[71] suggest possible strategies to increase the beneficial effects of motor training on function in the paretic hand (FIG. 1): enhancing excitability in the ipsilesional M1 and decreasing excitability in the contralesional M1. Neuromodulation of activity in the dorsal[58,62] and ventral[100] premotor cortices or the supplementary motor area are under active investigation.[31]

Enhancing excitability in the ipsilesional motor cortex

Both tDCS and rTMS have been used to enhance excitability in the ipsilesional primary motor cortex. Anodal tDCS applied to the ipsilesional M1 has been studied in patients with chronic stroke in sham-controlled double-blind crossover experimental designs.[95,101,102] In the first double-blind sham controlled study in 6 patients, each with a single ischemic subcortical cerebral infarct,[101] the authors documented transient improvements in performance of the Jebsen–Taylor hand-function test (JTT)[103] with one single session of stimulation but not with sham. This improvement was evident in all patients studied, representing approximately a 10% reduction in the time required to perform the JTT, and persisted for more than 30 minutes after the end of the stimulation period. The beneficial behavioral effect in this study was associated with increased motor cortical excitability and reduced intracortical inhibition in ipsilesional M1. Although no improvement was observed after sham stimulation, there was a trend toward a greater improvement in subtests of the JTT that emphasize fine motor control of the distal hand muscles, such as turning over cards and picking up objects with a spoon, compared with activities related with upper arm motor function. Improvements in the JTT are highly relevant to a stroke patient's ability to perform everyday activities and have been shown to correlate well with functional rehabilitation.[104–106]

In a study using a single session of rTMS in patients with chronic stroke, Kim et al.[89] showed that high-frequency rTMS (10 Hz) to the ipsilesional M1 resulted in a significantly larger increase in MEP amplitudes than sham rTMS; this increase was associated with an enhanced accuracy during performance of a finger motor sequence task. In a study performed in subacute instead of chronic stroke patients, with multiple sessions of rTMS applied to the ipsilesional M1, Khedr et al.[107] used rTMS (10 trains of 3 Hz stimulation, duration 10 seconds, with 50 seconds between each train, twice daily) combined with customary rehabilitative treatment for 10 days within the first 2 weeks after stroke. They reported performance improvements with rTMS relative to sham lasting for at least 10 days after the end of the treatment period.[107] None of the studies that stimulated the ipsilesional primary motor cortex reported complications other than transient headache.

Such studies have led to the proposal that repetitive stimulating sessions could elicit longer lasting effects than single applications, as well as the idea that association of cortical stimulation with motor training could enhance the benefit.

Decreasing excitability in the contralesional motor cortex

Based on the idea that interhemispheric interactions can influence motor performance,[108] it should be possible, in theory, to improve motor function in the paretic hand by decreasing excitability in the contralesional M1—possibly through modulation of inappropriate interhemispheric inhibition.[65] Studies in normal volunteers showed that decreasing excitability in one M1 results in increased excitability in the opposite M1[109,110] and even in performance improvements in motor function of the ipsilateral hand.[111] In patients with stroke, it was shown that cathodal tDCS applied to the contralesional M1 may improve performance in the paretic hand, possibly by suppressing the imbalance in interhemispheric inhibition proposed to interfere with stroke recovery in some patients.[95] Decreasing activity in the contralesional M1 with 1 Hz rTMS was recently found to decrease interhemispheric inhibition from the contralesional to ipsilesional hemisphere of chronic stroke patients[112]; the decrease in interhemispheric inhibition elicited by rTMS correlated with functional improvements in a finger pinch acceleration task. Another study, using low-frequency rTMS to the contralesional motor cortex, found behavioral improvements in the paretic hand in simple reaction time and on the Purdue Pegboard test.[113] In a study of 6 chronic stroke patients by Fregni et al.,[95] the effects of cathodal tDCS applied to the contralesional primary motor cortex was compared with the effects of anodal stimulation to the affected hemisphere and sham stimulation, again using the JTT time as the behavioral outcome measure. Their results for anodal tDCS to the affected hemisphere[95] were consistent with those of Hummel et al.[101] (Note, however, that the patient population studied by Fregni et al.[95] was subacute stroke patients more severely affected than those studied by Hummel et al.,[101] limiting to some extent the comparability of the 2 studies.) In that study by Fregni et al.,[95] cathodal stimulation to the contralesional M1 produced a significant improvement of 11.7% on motor performance relative to sham.

The therapeutic studies conducted in stroke patients thus far have been limited to interventions consisting of a single session of approximately 20 minutes of stimulation. It is likely that longer sessions or multiple applications could lead to longer lasting beneficial effects, as shown by Khedr et al.[107] using rTMS. Another potential advantage of this approach over stimulation of the ipsilesional M1 is that it is applied to healthy neural structures.

Although the majority of interventional studies of TMS in stroke patients have focused on motor function, some studies have sought to test the ability of decreasing activity in the contralesional hemisphere to improve language function, including nonfluent and global aphasia.[114,115] Overall, their findings further support the concept that repeated interventions (in this case, to decrease activity in the contralesional hemisphere) can lead to behavioral gains in speech function that remain stable over lengthy periods, possibly through modulation of inhibitory interhemispheric interactions. Interestingly, prior to the TMS intervention in one patient,[115] speech therapy had been discontinued due to lack of progress and poor prognostic indicators.

PERSPECTIVES

Studies of noninvasive brain stimulation have shown promising results thus far, but there are some limitations to be kept in mind. The studies were obtained in relatively small and selected groups of subjects, often with moderate remaining motor function. The magnitude of improvements reported so far ranged between 10% and 30%, and we do not know how long lasting they will prove to be. This issue could be addressed in future studies using multiple applications of tDCS or TMS.

It would be useful to determine the best parameters and type of experimental sham controls required to optimize and detect the effects. Similarly, we need to better understand the influence of lesion site, chronicity, and levels of impairment on the magnitude of the response to noninvasive stimulation, as well as on the duration of effects. More important, the behavioral endpoint measures in these studies have differed: some ecologically valid, others less so. In addition to this problem, it is conceivable that performance of different tasks engages activity in different neural networks after stroke, making comparisons across studies even more difficult.

In conclusion, TMS and tDCS are emerging as powerful tools for modulating brain activity and cognitive function in stroke patients, with the goal of contributing to rehabilitation. Larger scale double-blind sham-controlled clinical trials are needed to determine the validity of these novel interventions.

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