

Transcranial Direct Current Stimulation in Stroke Recovery

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Transcranial direct current stimulation (TDCS) is an emerging technique of noninvasive brain stimulation that has been found useful in examining cortical function in healthy subjects and in facilitating treatments of various neurologic disorders. A better understanding of adaptive and maladaptive poststroke neuroplasticity and its modulation through noninvasive brain stimulation has opened up experimental treatment options using TDCS for patients recovering from stroke. We review the role of TDCS as a facilitator of stroke recovery, the different modes of TDCS, and the potential mechanisms underlying the neural effects of TDCS.

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The concept of using therapeutic electricity on excitable tissues such as the brain is not new considering the attempts to cure epileptic disorders with electric catfish as early as the 11th century as noted by Priori.¹ After a serendipitous discovery of abnormal involuntary movements in patients treated with high-voltage transcranial electric currents, initial experiments by Hitzig in 1870 on dog cortex led to an interest in using electric currents to identify the cortical representations of limb movements as cited by Gross.² Electrosleep therapy, mentioned by Gilula and Barach,³ which later came to be known as “cranial electric stimulation,” has been used to treat sleep disorders and depression since 1902.

In the 1960s, Bindman et al⁴ performed experiments that resulted in long-lasting polarization effects following electric stimulation of the exposed motor cortex of animals, which led to a resurgence of studies exploring the clinical applications of electric stimulation, including the use of brain polarization in patients with depression. Although the investigations showed some benefits, replicating these beneficial effects in controlled settings yielded mixed results, which subsequently led to a diminished

interest in transcranial electric treatments. However, several years later, the effects of anodal direct currents on brain tissue in rats⁵ (such as increased accumulation of calcium ions, leading to increased cortical excitability, and evidence for intracerebral currents during electrosleep therapy studies in humans) prompted Priori and colleagues^{1,6} to develop a novel approach of noninvasive brain stimulation using weak direct currents, which came to be known as “transcranial direct current stimulation” (TDCS). Subsequent experiments by Nitsche and Paulus^{7,8} demonstrated modulating effects of anodal (increases cortical excitability) and cathodal (decreases cortical excitability) TDCS on brain tissue in which the effects surprisingly outlasted the duration of stimulation. Residual electrophysiologic effects were detectable up to 90 minutes and sensorimotor and cognitive effects up to 30 minutes after a 20- to 30-minute stimulation period.^{7,8} These early reports and others during the past 8 to 10 years have renewed the interest in the use of noninvasive regional brain polarization for various neurologic disorders. Current research studies make use of the blocking and depressing effects of cathodal TDCS to create temporary cortical dysfunctions (“virtual lesions”), which

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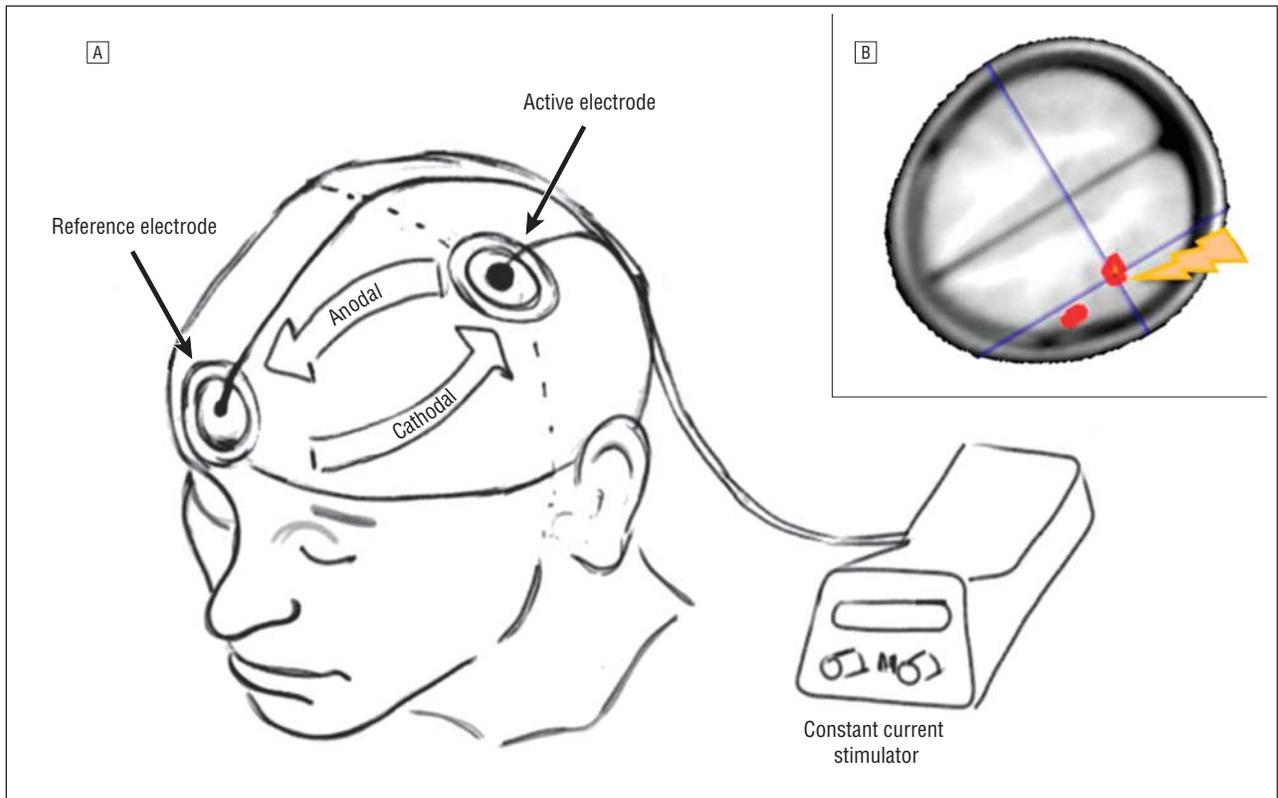


Figure 1. Transcranial direct current stimulation setup and montage. A, The setup using a mobile battery-operated direct current stimulator connected with 2 electrodes. One electrode (active) is positioned over C3 (corresponding to the precentral gyrus), and the reference electrode is positioned over the contralateral supraorbital region. If current flows from C3 to the supraorbital region, then the tissue underlying C3 is subjected to anodal (increase in excitability) stimulation. If current is reversed, then the tissue underlying C3 is subjected to cathodal (decrease in excitability) stimulation. B, Regional cerebral blood increases in the motor region underlying the electrode positioned over C3 after anodal stimulation. Regional cerebral blood was determined using a noninvasive arterial spin-labeling technique.¹¹

enables investigators to causally examine functions of cortical regions. Similarly, studies have examined whether anodal TDCS can be used to improve performance of certain sensorimotor or cognitive tasks (Vines et al^{9,10} provide an example of these 2 approaches).

MECHANISMS OF TDCS

The components required for TDCS include a constant current stimulator and surface electrodes soaked in isotonic sodium chloride solution. While constantly monitoring the resistance in the system, a constant current stimulator provides a steady flow of direct current (eg, 0-4 mA). Electrodes soaked in isotonic sodium chloride solution, which are applied and secured onto the scalp over desired areas such as the left or right precentral gyrus region (corresponding to C3 or C4 of the international 10-20 electroencephalographic system), form terminals relaying currents across the scalp and through the underlying brain tissue. The direction of the current flow determines the effects on the underlying tissue. With an active electrode over C3 or C4, a reference electrode over a control region (eg, supraorbital region), and current flowing from the active to the reference electrode, the excitability of the brain tissue under the anodal electrode is increased, and when the current flow is reversed, the excitability of the brain tissue under this electrode is decreased (the electrode that was previously the anode now

becomes the cathode) (Figure 1A). Once switched on, the constant current stimulator produces a transient tingling sensation under the electrode that fades off in 30 to 60 seconds, thereby making it ideal for use in blinded subjects (in sham-control studies) by turning it off after the initial sensory experience. McCreery et al¹² found that current densities below 25 mA/cm² did not cause brain tissue damage, and the protocols that apply 1 to 2 mA as in present-day studies fall well within these limits. Recent results of investigations on brain modeling and current density distribution suggest that, despite a fraction of the direct current being shunted through the scalp, TDCS carries adequate currents to the underlying cortex that are sufficient for neuronal excitability shifts.¹³ Preliminary results of our ongoing studies have shown that measures of cerebral blood flow can change in brain regions that are targeted by transcranial anodal direct current, providing further proof that transcranially applied direct currents can affect tissue excitability and regional blood flow as an indirect marker of change in regional tissue excitability (Figure 1B).

The advantages of TDCS over other noninvasive brain stimulation methods include its ease of use, large electrode size allowing effect over a larger neural network, sham mode allowing controlled experiments and randomized controlled clinical trials, and portability that makes it possible to apply stimulation while the patient receives occupational or physical therapy. Neverthe-

less, TDCS is limited by its poor temporal resolution and anatomical localization. Furthermore, interindividual variation in conductivity due to differences in hair, scalp, and bone composition can interfere with the current that is carried to the brain. Finally, although single and multiday sessions have been performed and found to be safe, the safety of prolonged periods of stimulation requires further studies.

By itself, TDCS provides a subthreshold stimulus that modulates the likelihood that neurons will fire by hyperpolarizing or depolarizing the brain tissue, without direct neuronal depolarization. The prolonged sensory, motor, and cognitive effects of TDCS have been attributed to persistent bidirectional modification of postsynaptic connections similar to long-term potentiation and long-term depression effects.^{5,7} Dextromethorphan, an *N*-methyl-D-aspartate antagonist, suppressed anodal and cathodal TDCS effects, strongly suggesting the involvement of receptors of the antagonist in both types of direct current-induced neuroplasticity.¹⁴ In contrast, carbamazepine selectively eliminated anodal effects.¹⁵ Because carbamazepine stabilizes the membrane potential through voltage-gated sodium channels (stabilizing the inactivated state of sodium channels), the results reveal that aftereffects of anodal TDCS require depolarization of membrane potentials.^{15,16} More studies are needed, particularly in humans, to verify the actions of TDCS on brain tissue, its underlying mechanism, and the associated behavioral and cognitive effects.

STROKE RECOVERY, NEUROPLASTICITY, AND EFFECTS OF BRAIN POLARIZATION

Stroke is the major cause of severe disability in the US population, with about half of the patients left with residual disabilities.¹⁷ Spontaneous recovery has been primarily attributed to neuroplasticity, which occurs predominantly by means of regeneration (eg, axonal and dendritic sprouting) and reorganization (eg, remapping of lesional area representations onto nonlesional cortex in the perilesional region or in the contralesional hemisphere). Functional magnetic resonance imaging studies have shown that early reorganization of the brain is associated with increased bihemispheric activation when the affected hand or arm is moved, which in stages of chronic stroke becomes more lateralized.^{18,19} The significance of contralesional (ipsilateral to the moving hand) activation during motor tasks involving the recovering hand or arm is uncertain. Explanations range from an epiphenomenon of recovery or an adaptive neuroplastic process to a sign of maladaptation that might interfere with the recovery process.

Early reactivation or overactivation of the remnant ipsilesional sensorimotor and premotor cortex generally correlates with good recovery.^{18,19} Whether the contralesional activation pattern (ipsilateral to the recovering hand or arm) is an epiphenomenon or a maladaptive phenomenon in the recovery process could be examined by blocking or depressing this activation using noninvasive brain stimulation methods such as TDCS. The electrophysiologic correlate of an apparent maladaptive activation pattern is an imbalance of interhemispheric inhibition due

to inhibition from the contralesional unaffected hemisphere onto the lesional hemisphere that is not balanced by a similar level of inhibition from the lesional hemisphere onto the contralesional normal hemisphere. This abnormal and imbalanced interhemispheric inhibition is the hypothetical model that underlies experimental therapy of applying anodal TDCS to the lesional hemisphere or cathodal TDCS to the nonlesional unaffected hemisphere.

EXPERIMENTAL ANIMAL STUDIES

Spontaneous, training-induced, and postpolarization neuroplasticity with or without physical rehabilitation has been studied in primates and in rodent brain models. Factors such as delay between the stroke and the time of initiation of therapy—as well as the type (monopolar or bipolar), frequency, and duration of the stimulation—have different outcomes on motor improvement, remapping of cortical representation, and overall functional outcomes.²⁰⁻²² For example, there was a significant difference in sensorimotor improvement in recovering rats receiving 50-Hz direct cortical stimulation compared with those receiving 250-Hz stimulation or no stimulation at all.²⁰⁻²² Histologic analysis of brains of these animals that received 50-Hz stimulation revealed a significantly higher surface density of microtubule-associated protein 2 in the perilesional cortex, which is typically associated with high dendritic activity.²² Most experimental animal studies have shown that rehabilitation-dependent improvement in motor performance is associated with remapping of movement representations toward the perilesional motor cortices and seems to be significantly enhanced when cortical stimulation is combined with rehabilitative motor training in the recovery phase.^{21,23} Combining peripheral and central stimulation might lead to an increase in synaptic plasticity modulated by depolarization-induced intracortical connectivity. Monopolar and bipolar currents showed significant benefits in increasing perilesional movement representations.²⁰ Compared with nonstimulated rats, cortically stimulated rats maintained their performance improvements for days without any intervening decline.²¹

HUMAN STUDIES

Studies in humans can be divided into invasive and noninvasive brain stimulation studies and further into those that are or are not coupled with simultaneous physical or occupational therapy. Epidural electric stimulation around a functional magnetic resonance imaging “hot spot” in the perilesional area, coupled with simultaneous occupational therapy, has shown benefits in pilot investigations.²⁴ However, the early benefits seen in the uncontrolled and unblinded phase 1 and phase 2 studies were not replicated in a recently concluded randomized controlled clinical trial²⁵ comparing the effects of combined epidural stimulation and occupational therapy with the effects of occupational therapy alone.

Noninvasive brain stimulation in humans has been performed with transcranial magnetic stimulation (TMS) and recently with TDCS. In this review, we will focus on TDCS studies. With its filtered current, TDCS may have some

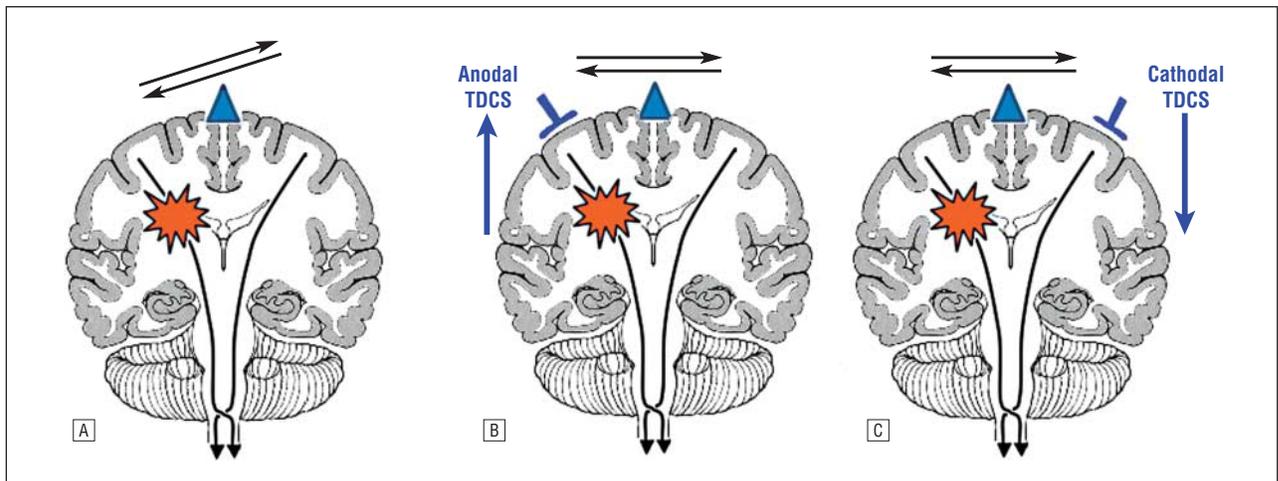


Figure 2. Brain model of imbalanced interhemispheric inhibition and the therapeutic options to ameliorate this imbalance. The balance of interhemispheric inhibition becomes disrupted after a stroke (A). This leaves the healthy hemisphere in a position in which it could exert too much of an unopposed or imbalanced inhibitory effect on the lesional hemisphere and possibly interfere in the recovery process of the affected hemisphere. There are 2 possible ways to ameliorate this imbalance, namely, upregulation of the excitability in the affected (lesional) hemisphere (B) or downregulation of the excitability in the unaffected (normal) hemisphere (C). TDCS indicates transcranial direct current stimulation.

advantages over direct cortical stimulation by affecting a wider region of brain involving not only primary motor cortex but also premotor, supplementary motor, and somatosensory cortices, all of which have been shown to have a role in the recovery process in various studies.^{18,19} Moreover, noninvasive transcranial stimulation is portable, is less risky than direct cortical or epidural stimulation, and can be performed on an outpatient basis, with optimal montage of electrodes suited to individual subjects.

Two modes of TDCS have been used in human stroke rehabilitation studies, namely, anodal stimulation (increase in excitability) of the lesional hemisphere (**Figure 2**) and cathodal stimulation (decrease in excitability) of the contralesional hemisphere. Proof-of-principle studies have been performed for both of these approaches using TMS and TDCS. These studies mostly applied a single session of TMS or TDCS and evaluated the effects, comparing performance in preintervention and postintervention batteries of motor assessments. Effects of multiple sessions are being studied. Preliminary findings of an ongoing trial at our institution involving 5 days of combined TDCS with occupational therapy in a cross-over sham-control study²⁶ suggested significant improvement in motor outcomes that lasted for at least 1 week. However, results of this cathodal TDCS study (stimulation applied to the contralesional hemisphere) contrast with those of an anodal TDCS study by Hesse et al,²⁷ who subjected patients after subacute stroke to multiple sessions of anodal TDCS (applied to the lesional hemisphere) in combination with a robot-assisted arm training protocol but failed to find significant motor improvements. These differences between cathodal stimulation to the unaffected hemisphere and anodal stimulation to the lesional hemisphere may be due to factors such as extent of the lesion, amount of cortical involvement, or involvement of the pyramidal tract on the lesional hemisphere. Further studies, and possibly direct contrasts between cathodal and anodal stimulation approaches, are needed to explore these issues. Previous findings in pa-

tients with chronic stroke using behavioral variables and TMS as a diagnostic tool have shown that anodal TDCS applied to the lesional motor region is associated with significant improvements in motor tasks, and the improvements correlated with the increase in excitability of the lesional hemisphere as indicated by a rise in the slope of the recruitment curve and a reduction in the short-interval intracortical inhibition as evidenced by TMS.²⁸ Similar findings have recently been made in our group by applying cathodal stimulation to the contralesional hemisphere in patients with chronic stroke; improvements in motor tasks correlated with a rise in the slope of the recruitment curve in the affected hemisphere and a decrease in the activation of the contralesional hemisphere as revealed by analysis of functional magnetic resonance imaging data.²⁶ Future studies might be able to use pretherapy assessments (eg, lesion size and location, integrity of the pyramidal tract, and the presence of abnormal interhemispheric inhibition) to tailor stimulation variables to patients after stroke. Such variables include mode of the stimulation (eg, anodal vs cathodal), strength of the stimulation, region of the brain to which stimulation should be delivered, and the extent of this region that is being stimulated. Transcranial direct current stimulation of the unaffected hemisphere may have the following inherent advantages over stimulation of the affected hemisphere: normal topography, intact intracortical connections, less risk of triggering a seizure ("scar epilepsy"), and reliance on a model of distribution in current density that is not disturbed by a lesion. Apart from the site of stimulation and the lesion size and location, many other factors can contribute to variability in natural and facilitated stroke recovery studies. Among others, these include age, sex, severity of the initial impairment, hemisphere affected (right vs left and dominant vs nondominant), lesion site (eg, cortical or subcortical vs deep white matter lesions), and relation between lesion location and retained pyramidal tract. The integrity of the pyramidal tract as examined using diffusion tensor imaging or as indicated by the presence of

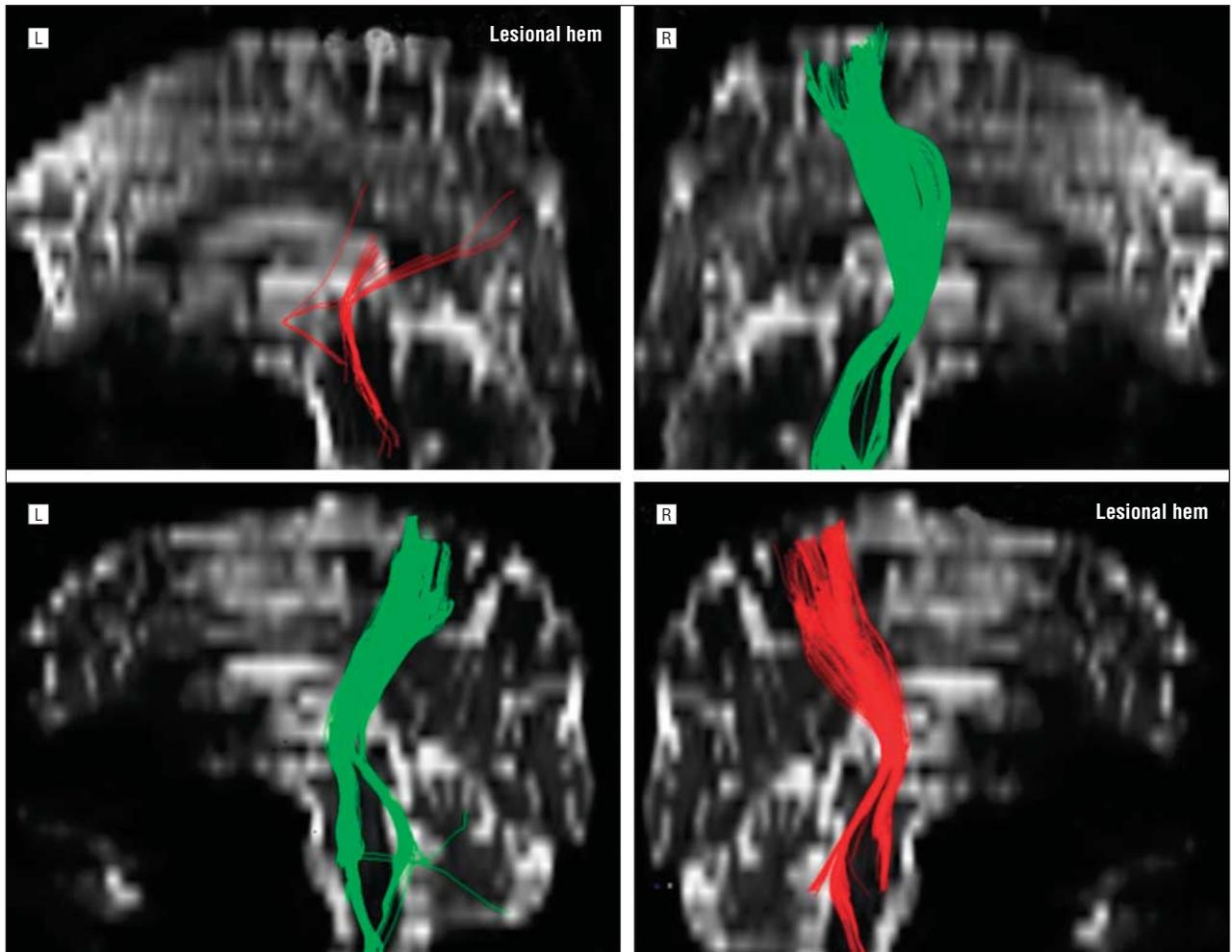


Figure 3. Diffusion tensor imaging and stroke recovery potential. Two patients are shown with their representative corticospinal tract (CST) fibers that originate from the white matter underlying the precentral gyrus and travel through the internal capsule into the brainstem. The CSTs of the lesional hemispheres (lesional hemispheres) differ between the patients. Patient 1 (top row) shows a severely reduced number of fibers, which do not seem to originate from the dorsal part of the motor region (hand or arm region of the precentral gyrus) but still show a path through the posterior limb of the internal capsule into the brainstem, while patient 2 (bottom row) has a mild reduction in the number of CST fibers in the lesional hemisphere but otherwise shows similar CST origin and descent between the lesional and normal hemispheres. The improvement after transcranial direct current stimulation was pronounced in patient 1 with an intact pyramidal tract but was only minimal in patient 2 with the disrupted pyramidal tract. L indicates left; R, right.

motor-evoked potentials in the affected hand is an important determinant of recovery and a predictor of stroke recovery potential.

Figure 3 shows imaging in 2 patients with incomplete recovery. Both patients underwent cathodal TDCS to their unaffected hemisphere in combination with simultaneous occupational therapy. One patient had pronounced improvement, while the other patient had only minimal improvement. Although the patient with prominent improvement had maintained an intact pyramidal tract (but a reduced number of fibers) in the lesional hemisphere, the patient with only minor improvement had a disrupted pyramidal tract. This highlights the importance of pyramidal tract integrity and appropriate selection of candidates for experimental interventions.

The magnitude of improvement that can be seen after combined peripheral and central stimulation has varied among studies and is dependent on the number of combined peripheral and central brain stimulation sessions a patient undergoes. In our experience, a 5-day treatment trial of central and peripheral stimulation might lead

to at least a 20% change in the upper extremity Fugl-Meyer score in those patients who have incomplete recovery but still have intact pyramidal tract fibers.²⁶

TDCS IN COMBINATION WITH REHABILITATIVE THERAPY

The effects of noninvasive brain stimulation on stroke recovery might be enhanced by combining it with peripheral stimulation using neuromuscular facilitation techniques as applied in routine rehabilitative therapy or other sensorimotor activities. Initial pilot and proof-of-principle single-session studies^{27,28} using TDCS alone have shown significant short-lasting excitability shifts and motor improvements. More recent studies^{26,27} have combined brain stimulation with simultaneous peripheral stimulation to further enhance the facilitating effect of noninvasive brain stimulation, with the idea being that combined peripheral and central input can enhance synaptic plasticity and skill relearning. Motor skill learning has been shown to produce changes similar to long-

term potentiation and long-term depression in the primary motor cortex in animal investigations.²⁹ Similar changes were seen following TDCS applied to the motor cortex in animal experiments.⁵ It is possible that combining the effects of these 2 interventions (TDCS and rehabilitative therapy) can potentiate relearning of motor skills to a level unattained by either intervention alone. This is supported by the fact that paired associative brain stimulation and repetitive peripheral nerve stimulation generated motor-evoked potentials and improved motor performance to a greater magnitude than that obtained by cortical stimulation alone.³⁰

SUMMARY

A safe, portable, noninvasive brain stimulation technique, TDCS is capable of modulating the excitability of targeted brain regions by altering neuronal membrane potentials based on the polarity of the current transmitted through the scalp via sponge electrodes. Anodal stimulation increases cortical excitability in the stimulated brain tissue, while cathodal stimulation decreases it. Corresponding behavioral effects have been seen if the behavior tested draws on the region that is stimulated. Transcranial direct current stimulation has enormous clinical potential for use in stroke recovery because of its ease of use, noninvasiveness, safety (does not provoke seizures), and sham mode (important for controlled clinical trials) and because of the possibility to combine it with other stimulation or stroke recovery-enhancing methods (eg, simultaneous occupational and physical therapy). If results of pilot and proof-of-principle studies show long-lasting benefits and can be replicated, TDCS may become an important adjuvant therapy in routine rehabilitative procedures in acute and chronic stroke settings.

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