EXPERT REVIEWS

Transcranial direct current stimulation: a noninvasive tool to facilitate stroke recovery

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Electrical brain stimulation, a technique developed many decades ago and then largely forgotten, has re-emerged recently as a promising tool for experimental neuroscientists, clinical neurologists and psychiatrists in their quest to causally probe cortical representations of sensorimotor and cognitive functions and to facilitate the treatment of various neuropsychiatric disorders. In this regard, a better understanding of adaptive and maladaptive plasticity in natural stroke recovery over the last decade and the idea that brain polarization may modulate neuroplasticity has led to the use of transcranial direct current stimulation (tDCS) as a potential enhancer of natural stroke recovery. We will review tDCS's successful utilization in pilot and proof-of-principle stroke recovery studies, the different modes of tDCS currently in use, and the potential mechanisms underlying the neural effects of tDCS.

Historical overview

The idea of 'therapeutic electricity' is relatively old if we consider the attempts to cure neurologic disorders using electric fish applied to the head [1]. Eduard Hitzig (1867) was one of the pioneers to test a constant current stimulator on his patients with depressive illnesses. Incidentally, in addition to the beneficial effects, he found that current sent through the skull of a patient produced involuntary eye movements. In 1870, he, along with anatomist Gustav Fritsch, studied the effects of galvanic stimulation on various regions of a dog's cortex to ascertain whether these effects were central or peripheral in origin. They found that electrical stimulation of different cortical areas gave distinct responses in the contralateral limb and ablation of these areas led to corresponding weaknesses [2,3]. In 1926, Bishop and Erlanger studied the effects of anodal polarization on motor neurons and found increases in the potential difference across the nerve sheath, the amplitude of response to stimulation and the duration of the spike and a decrease in the absolute refractory period (ARP). Cathodal polarization had the opposite effects [4,5]. In the 1960s, Bindman showed that potential gradients produced by currents of the order of 0.1–0.5 µA were sufficient to produce

neuronal excitability shifts in rat cortex [6,7]. The change in evoked and spontaneous activity produced by polarizing currents could last for many hours after the current was switched off. This observation evoked much interest as it seemed possible to modulate long-lasting changes in neural excitability through brain polarization of relatively short duration. They also showed that the motor potentials evoked in the contralateral limb were increased by anodal stimulation and decreased by cathodal stimulation.

Therapeutic application of brain stimulation techniques in psychiatry began in the 1960s. Lippold and Redfearn, influenced by their findings of persistent excitatory aftereffects of surface-positive cortical polarization in rats with Bindman, found significant benefits of brain polarization in depressed patients who were resistant to other forms of treatment, including electroconvulsive therapy (ECT) [7–9]. They used direct currents of 50–500 µA with the active electrode above the eyebrows and the indifferent electrode on the leg. They reported that scalp anodal currents induced an increase in alertness, mood and motor activity, whereas cathodal polarization produced quietness and apathy in healthy subjects [8,9]. Costain followed-up with controlled trials in similar settings, again

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confirming significant effects with this type of intervention [10], as did other groups over the next 6–8 years. However, interest in noninvasive electrical brain stimulation faded away as subsequent groups of investigators failed to replicate earlier results [11–13].

Re-emergence of transcranial direct current stimulation

Armed with newer diagnostic modalities, such as transcranial magnetic stimulation (TMS), to assess the neural effects of transcranial direct current stimulation (tDCS) and inspired by the conductivity of direct current (DC) across the skull, Priori *et al.* tested the effects of DC on cortical excitability using TMS [1,14]. Together with Nitsche and Paulus this group set forth a revival of tDCS [15–18]. Nitsche and Paulus showed that cathodal polarization reduced the size of the TMS-induced motor evoked potentials (MEP), indicating a reduced motor cortex excitability [15–18], while anodal stimulation increased the size of the MEP, suggesting increased excitability of the motor cortex and corticospinal tracts. The duration of these effects outlasted the duration of stimulation. Using TMS it was shown that 10–20 min of tDCS over the motor cortex would lead to an increase in excitability up to 150%, lasting for around 90 min [16,17]. These early reports, and others over the last 8–10 years, have renewed a widespread interest in transcranial electrical stimulation and its application in various fields of neurology.

Current research explores the effects of cathodal tDCS as a modality to create temporary cortical dysfunctions ('virtual lesions') in order to causally probe cortical sensorimotor representations and cognitive operations [19,20]. Similarly, anodal tDCS has been used to examine whether the performance of a particular sensorimotor skill or cognitive operation that is linked to the stimulated brain region can be enhanced temporarily. Following cathodal stimulation, detriments in performance have been observed in motor skills after motor cortex stimulation [19], auditory memory functions after inferior parietal stimulation [20], or tactile perception after somatosensory cortex stimulation [21]. Correspondingly, improvements in performance after anodal stimulation have been shown in implicit motor learning [22], visuomotor coordination [23] and probabilistic classification [24], although there have also been studies that found a cathodal effect (detriment in performance) but no enhancement effects after anodal stimulation when compared with sham stimulation [21]. Even though anodal and cathodal tDCS have been associated with increased or decreased excitability, these effects might be region specific and could possibly be related to the orientation of fibers originating from, or connecting to, a stimulated region. More research is needed to determine the influence of regional connectivity and fiber composition

on the effects of tDCS. However, the influence of tDCS on motor cortex seems to be uniform across studies, with anodal stimulation increasing and cathodal stimulation decreasing excitability. These effects are the basis for the use of tDCS as a facilitating tool in stroke recovery studies.

Method of tDCS

The components required for tDCS include a constant current stimulator and surface electrodes. A constant current stimulator can be either battery operated or connected to a power source. It should provide an uninterrupted direct current supply through the anodal and cathodal ends, while monitoring the system for any change in resistance resulting from dryness of the electrodes, loss of contact or other causes. Current stimulators available have voltage setting from 0 to 4 mA and can supply up to 80 mA/min per session. Saline-soaked electrodes with variable surface areas (areas of 5–50 cm^2 have been reported) are placed on the desired region of interest (e.g., C3 or C4 for left or right primary motor cortex, respectively). The direction of the current flow determines the effect on the underlying tissue. If the positive electrode is placed over C3 or C4 and a reference electrode, for example, over a supraorbital region, which acts as a terminal to complete the circuitry, then the brain tissue underlying the C3 or C4 region receives anodal stimulation. If the current is reversed, the tissue underlying C3 or C4 is subject to cathodal stimulation (**Figure 1**).

Location of the reference electrode is important in both situations as it can influence the underlying tissue. In order to reduce any unwanted effects on brain tissue by the reference electrode, this electrode is frequently chosen to be in the supraorbital region
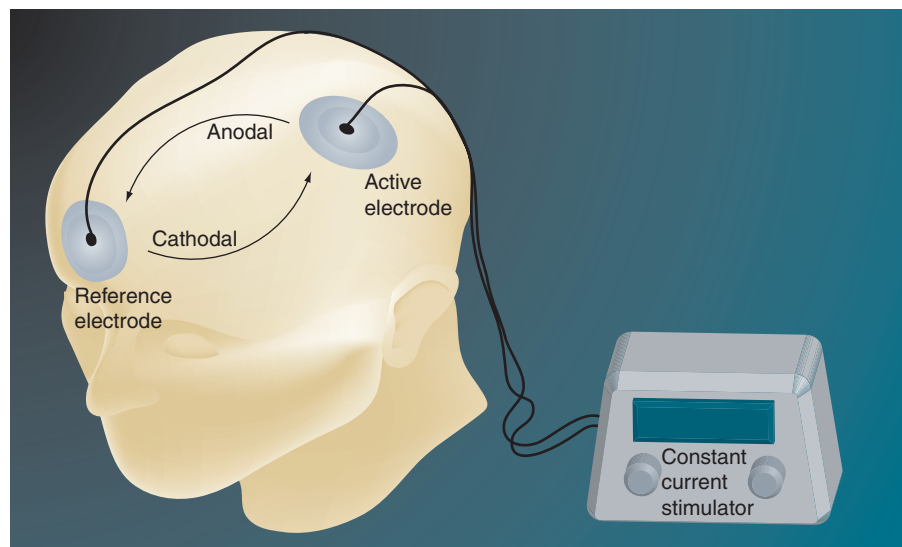

Figure 1. Transcranial direct current stimulation set-up. This figure shows a mobile, battery-operated direct current stimulator connected with two electrodes. One electrode (active) is positioned over C3 (corresponding to the precentral gyrus) and the reference electrode is positioned over the contralateral 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.

or outside the skull, over the collarbone or the chest. However, one has to consider the location of the reference electrode carefully, since at least one report has shown that placing an electrode at a position that involves passage of current through the brainstem carries a risk of respiratory depression [7]. Once the constant current stimulator is switched on, subjects usually have a tingling, itching or a warming sensation under and around the electrodes as the current ramps up. This usually fades away in 30 s to 1 min owing to tolerance. Current density might also have an effect on the perceived intensity, and how quickly this tingling/itching/warming sensation might fade away. However, this transient sensation enables tDCS to have a sham mode, which entails turning off the current stimulator, unnoticed by the subject, after letting it ramp up. This gives the subject this initial experience of a tingling sensation, which has been shown to be undistinguishable from the initial sensory experience of real stimulation by research subjects [25].

Transcranial direct current stimulation has been shown to be a relatively safe intervention [26] with side effects mostly limited to focal tingling, itching and at most a local erythema. Nitsche and colleagues described general safety limits for tDCS [27]. They identified 'current density' and 'total charge' as the most important parameters for judging the safety of tDCS studies. McCreery and colleagues found that current densities below 25 mA/cm^2 do not cause brain tissue damage [28]. The current density in protocols that apply 1 mA through an electrode with a size of 15–25 cm^2 is approximately 0.1 mA/cm^2, which translates into 0.004% of the magnitude at which stimulation begins to be potentially dangerous for tissue. Yuen and colleagues found that no brain tissue damage occurs for a total charge less than 216 C/cm^2 [29]. Our own protocols typically involve a maximum total charge of 2.4 C/cm^2, approximately 0.01% of the minimum magnitude at which tissue damage can occur. The stimulation protocols that have been used recently with 1–2 mA current strength applied for 20–30 min fall well within the safety limits.

Mechanism of tDCS

Transcranial direct current stimulation provides a subthreshold stimulus that modulates the likelihood that neurons will fire by hyperpolarizing or depolarizing the brain tissue, without direct neuronal depolarization [7,17]. The prolonged sensory, motor and cognitive effects of tDCS have been attributed to a persistent, bidirectional modification of post-synaptic connections similar to long-term potentiation (LTP) and long-term depression (LTD) effects [30–32]. Dextromethorphan, an NMDA antagonist, suppressed both anodal and cathodal tDCS effects, strongly suggesting the involvement of NMDA receptors in both types of DC-induced neuroplasticity. By contrast, carbamazepine selectively eliminated anodal effects. Since carbamazepine stabilizes the membrane potential through voltage-gated sodium channels (stabilizing the inactivated state of sodium channels), the results reveal that the after effects of anodal tDCS require a depolarization of membrane potentials [33]. Ardolino and colleagues also proposed a nonsynaptic mechanism involving changes in membrane excitability and ionic

shifts [34]. Nevertheless, more studies are needed, particularly in humans, to verify the effects of tDCS and to better understand the underlying mechanisms. Recent studies on brain modelling and current density distribution have suggested that, in spite of a large fraction of the direct current being shunted through the scalp, tDCS carries adequate currents to the underlying cortex, modulating neuronal excitability, and corresponding regional blood flow changes have been seen using noninvasive arterial spin-labeling techniques [35–37].

Stroke recovery, neuroplasticity & brain polarization effects

Stroke is the major cause of severe disability in the population of the USA, with approximately half of all stroke victims being left with residual disabilities [37]. In stroke survivors a dynamic neuroplastic process is initiated that involves an increase in perilesional excitability mediated by excitatory neurotransmitters in the acute and subacute phase. This subsides on course to a chronic phase that is more characterized by changes in the intracortical and interhemispheric inhibition imbalance, which could facilitate or hinder natural recovery [38].

Spontaneous recovery has been attributed primarily to neural plasticity in both perilesional areas and the contralesional hemisphere, with regeneration and reorganization being the major mechanisms of this plasticity. Regeneration involves axonal and dendritic sprouting and formation of new synapses [39]. Stroke by itself provides a permissive environment for neuronal regeneration in the perilesional cortex by inducing the production and release of various growth factors [40]. Reorganization involves remapping of lesional area representations onto nonlesional cortex, either in the perilesional cortex or in the contralesional hemisphere. However, neuroplasticity after a stroke might not always be adaptive or facilitate recovery. Plasticity may also be maladaptive, leading to excitability changes or a rewiring pattern that might interfere with recovery. Aberrant activation patterns as seen with brain imaging studies, as well as excitability shifts in TMS studies, might be indicative of this maladaptation. Furthermore, the recovery process might also be influenced by various internal and external factors ranging from the type, location, extent and severity of the ischemic lesion to patient factors, such as age, sex and handedness for example. The effects of these factors on natural recovery or recovery potential of each patient have not been fully examined.

Functional MRI (fMRI) studies have shown that early poststroke reorganization of the brain is generally associated with enhanced bihemispheric activation patterns, suggestive of increased compensatory activity in the perilesional and contralesional motor and supplementary motor cortices [41–45]. Correspondingly, TMS studies have shown greater excitability in the contralesional sensorimotor cortex as well as adjacent areas with reduced resting motor thresholds and intracortical inhibition [46–48]. In addition, TMS studies have shown that the contralesional hemisphere is disinhibited from the counterinhibitory influence of the opposite motor cortex following stroke [49,50]. This could lead to an unbalanced interhemispheric inhibition from the normal to the lesional hemisphere, which could further

interfere with the recovery process after a stroke [50,51]. fMRI studies examining natural recovery have shown that good recovery is associated with increased activation of the ipsilesional sensorimotor system, but frequently one can also see activation of the contralesional (ipsilateral) sensorimotor system (**Figure 2A**). The significance of contralesional (ipsilateral to the moving hand) activation during motor tasks involving the recovering hand/arm has not been determined [44,52–56]. Explanations range from an epiphenomenon of recovery, to an adaptive neuroplastic process, to a sign of maladaptation that might possibly interfere with the recovery process. In this scenario, tDCS emerged as an ideal tool as it can noninvasively exert an inhibitory influence on the contralesional motor cortex and/or an excitatory influence on the perilesional motor regions, potentially upregulating residual activity using anodal stimulation. In addition, the polarizing effects of tDCS might also have long-term modulating effects on neuroplasticity similar to those described by direct cortical stimulation in experimental animal studies.

Experimental animal models have been used to study the process of postinfarct neuroplasticity and polarization induced recovery. Although noninvasive methods (i.e., tDCS) in humans and invasive methods (i.e., direct cortical stimulations) in experimental animal models differ in the way that the current is injected into the brain, the underlying effects may be similar. Further physiological studies in both humans and experimental animal models are necessary to examine and determine whether these two models are similar, and whether postinfarct neuroplastic changes in experimental animal models and peri-infarct direct cortical stimulation can help in understanding and developing new therapeutic options for post-stroke recovery in humans.

Direct cortical stimulation studies in experimental animal models & human stroke

Spontaneous, training-induced and postpolarization neuroplasticity with or without physical rehabilitation have been studied in primates and rodent brain models [57–62]. Factors such as the delay between the stroke and the time of initiation of therapy, as well as the type (monopolar and bipolar), frequency and duration of the stimulation all had different effects on remapping cortical representation of limbs and movements and on overall functional outcomes [57–62]. For example, there was a significant difference in sensorimotor improvement in recovering rats receiving 50 Hz direct cortical stimulation compared with those receiving either 250 Hz stimulation or no stimulation at all [61]. Histological analysis of the brains of these animals revealed a significantly higher surface density of dendritic microtubule-associated protein 2 in the perilesional cortex, which is typically associated with high dendritic activity [61]. Most experimental animal studies have shown that rehabilitation-dependent improvement in motor performance is associated with remapping of movement representations in the perilesional motor cortices. Cortical stimulation along with rehabilitative motor training seems to be able to facilitate this recovery process [58–61]. Both monopolar and bipolar currents showed significant benefits in increasing perilesional movement representations [61]. It was also observed that, in comparison to the nonstimulated groups, the cortically stimulated rats maintained their performance improvements for days without any intervening decline [59]. Successful results in animal studies led to interest in modulating brain activity in human stroke victims. Epidural stimulation around an fMRI 'hotspot' in the perilesional area, coupled with simultaneous occupational therapy, has shown benefits in pilot studies [63,64]. However, the early benefits seen in the uncontrolled and unblinded Phase I and Phase II studies were not replicated in a recently concluded, randomized, controlled clinical trial (EVEREST) comparing the effects of combined epidural stimulation against occupational therapy alone for 4 weeks [65].

Current trends in tDCS & human stroke rehabilitation

Two modes of tDCS have been used in human stroke rehabilitation studies: anodal tDCS applied to the lesional motor areas or cathodal tDCS to the contralesional motor cortex (**Figure 3**). The underlying theory to support both of these approaches is based on the hypothesis that a focal lesion disrupts the balanced interhemispheric inhibition and tDCS facilitates a shift of the imbalance
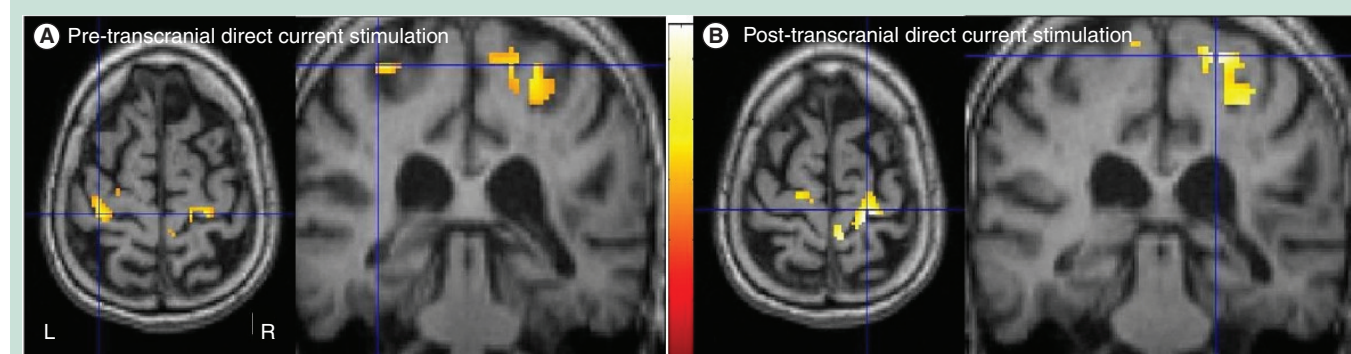

Figure 2. Functional MRI (fMRI) activation pattern in stroke recovery. fMRI studies in patients recovering from a stroke have shown that the ipsilateral (to the moving hand) sensorimotor cortex can become active when a patient performs a movement with their recovering hand. The patient in **(A)** had a stroke in the right hemisphere and was asked to move his left wrist, which is the recovering wrist; fMRI shows activation of the contralateral (to the moving hand) motor cortex as well as the ipsilateral motor cortex. **(B)** Applying cathodal stimulation to the nonlesional motor cortex (the motor cortex that activated when the recovering wrist was moving) significantly decreased the activation on the ipsilateral site and was associated with an improvement in this patient's functional motor status.

towards a more balanced state. Some support for this disturbance in interhemispheric inhibition comes from electrophysiological and imaging studies, which were referenced previously. Proof-of-principle studies have been performed for both of these approaches with TMS [66–68] as well as tDCS [69–73]. These studies mostly applied a single session of either TMS or tDCS and evaluated the effects comparing performance in pre- and post-intervention batteries of motoric tests. Some studies that have used tDCS to facilitate the recovery process are summarized in Table 1.

Effects of multiple sessions have been undertaken more recently or are ongoing [70,71]. Studies in chronic stroke patients using behavioral parameters and TMS as a diagnostic tool have shown that anodal tDCS of motor regions of the affected hemisphere is associated with improvements in functional tasks and motor parameters, which correlated with the increase in excitability of the lesional hemisphere as indicated by the rise in slope of the recruitment curve and a reduction in the short interval intra-cortical inhibition (SICI) as evidenced by TMS [73,74]. Similar findings have been made recently with regard to cathodal inhibition of the contralesional, unaffected hemisphere [71]. Preliminary analyses of an ongoing trial in our own institution revealed that 5 days of tDCS combined with occupational therapy in a crossover, sham-controlled study lead to a significant improvement in motor outcomes that lasted for at least 1 week [71]. The improvement in motor outcomes correlated with a decrease in the contralesional excitability as determined by the slope of the input–output curve of the contralesional hemisphere. Furthermore, in some subjects, following cathodal tDCS of the contralesional (unaffected) hemisphere there was a decrease in the ipsilateral activation

when the recovered hand was moving as determined by fMRI (Figure 2B). In contrast to these results, a pilot study by Hesse et al., in which patients underwent multiple sessions of anodal tDCS (stimulation applied to the lesional motor regions) combined with robot-assisted arm training protocol in subacute stroke patients, failed to find overall significant improvement even though three out of ten subjects showed significant motor improvements [70]. The currents used by Hesse et al. [70] were of higher magnitude (1.5 mA) than in some other studies, but the duration of stimulation was only 7 min, which differed from parameters in our own study (1 mA for 30 min) or earlier studies by Hummel et al. (1 mA for 20 min). Considering that the patients enrolled in the study by Hesse et al. had severe disabilities with FM scores of less than 18 and might not have an intact pyramidal tract [70], it might be important to consider the integrity of the pyramidal tract in future studies, as a possible determinant of a therapeutic response to any kind of experimental intervention (Figure 4).

Since there has been some support for both cathodal stimulation to the nonlesional hemisphere and anodal stimulation to the lesional hemisphere, it remains unclear whether the stimulation of the affected or the nonaffected hemisphere has advantages or disadvantages, since no direct, head-to-head comparisons have been performed. tDCS applied to the nonaffected hemisphere may have some advantages over tDCS applied to the affected hemisphere, since the current density distribution is not disturbed by an underlying stroke with nonhomogenous tissue and there might be a lesser risk of triggering a 'scar epilepsy'. Obviously, there are several other factors that could explain variability in tDCS outcomes, such as the hemisphere affected (right vs left, dominant vs

Table 1. Synopsis of stroke recovery studies that used transcranial direct current stimulation.

Study	Intervention	Current	Subjects/design	Results	Ref.
Hummel et al. (2005)	Anodal tDCS over lesional motor region	1 mA for 20 min	n = 6; crossover	Significant improvement in JTT performance after real tDCS compared with sham	[72]
Hummel et al. (2006)	Anodal tDCS of lesional motor region	1 mA for 20 min	n = 11; crossover	Anodal tDCS shortened reaction times and improved pinch force in the paretic hand relative to sham stimulation	[73]
Hesse et al. (2007)	Anodal tDCS of lesional motor region	1.5 mA for 7 min	n = 10; uncontrolled	Arm function of three patients (two with a subcortical lesions) improved significantly, with UEFM scores increasing from 6 to 28, 10 to 49 and 11 to 48. In the remaining seven patients (all with cortical lesions), UEFM did not increase significantly	[70]
Fregni et al. (2005)	Cathodal tDCS of contralesional motor region; Anodal tDCS of lesional motor region	1 mA for 20 min	n = 6; crossover	Both cathodal stimulation of the contralesional hemisphere and anodal stimulation of the lesional hemisphere were associated with significant improvement in JTT compared with sham stimulation	[69]
Nair et al. (2008)	Cathodal tDCS of contralesional motor region	1 mA for 30 min	n = 10; crossover	Cathodal tDCS yielded significant improvement in ROM and UEFM compared with sham tDCS; improvement in ROM correlated with a decrease in contralesional hemisphere excitability as assessed by TMS	[71]

JTT: Jebson Taylor Hand Function Tests; ROM: Range of movement; tDCS: Transcranial direct current stimulation; TMS: Transcranial magnetic stimulation; UEFM: Measure of neurological and motor function.
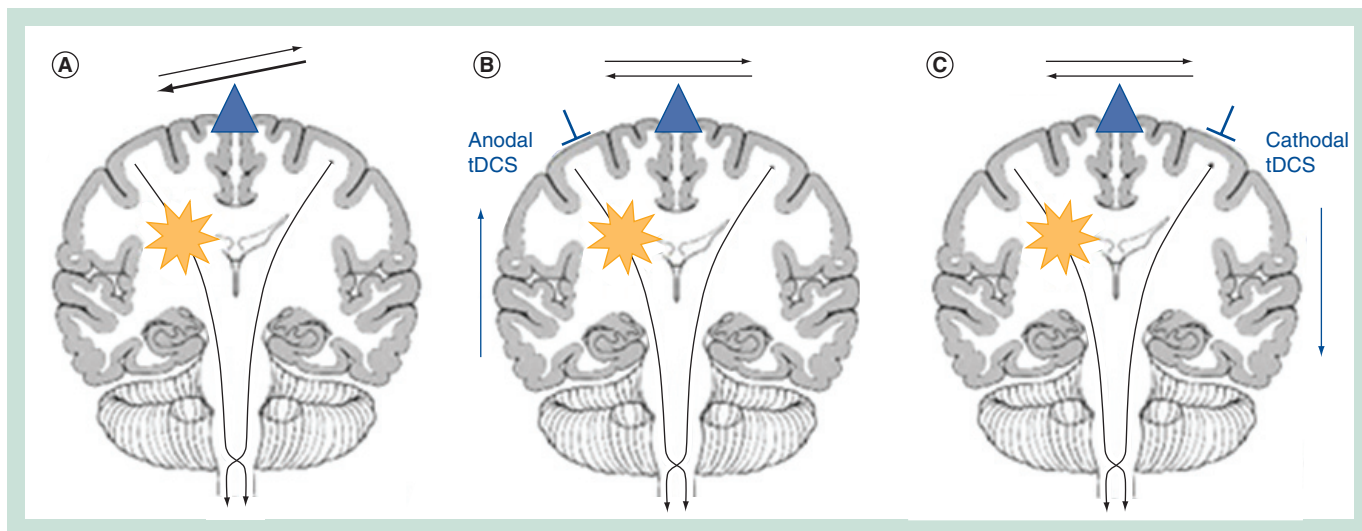
Figure 3. Brain model of abnormal interhemispheric inhibition and the therapeutic options to ameliorate this imbalance.
(A) The balance of interhemispheric inhibition becomes disrupted after a stroke. This leaves the healthy hemisphere in a position that it could exert too much of an unopposed influence onto the lesional hemisphere and possibly interfere in the recovery process. There are two possible ways to ameliorate this process: either **(B)** the excitability in the affected (lesional) hemisphere is upregulated or **(C)** the excitability in the unaffected (normal) hemisphere is downregulated.

nondominant), lesion site (e.g., cortical/subcortical vs deep white matter lesions), lesion size, the relation between lesion location and intact pyramidal tract, severity of the initial impairment, age or gender, among others. FIGURE 4 shows two patients with incomplete recovery. Both patients underwent cathodal tDCS to their nonaffected hemisphere in combination with simultaneous occupational therapy. One of the patients had a prominent improvement while the other had only minimal improvement. While the patient with prominent improvement maintained an intact pyramidal tract (although a reduced number of fibers) in the lesional hemisphere, the patient showing only minor improvements had a disrupted pyramidal tract (FIGURE 4). This highlights the importance of pyramidal tract integrity and appropriate selection of candidates for testing noninvasive experimental interventions.

tDCS in combination with rehabilitative therapy

Several recent studies have combined brain stimulation with rehabilitative therapy to further enhance the facilitating effect of noninvasive brain stimulation [70,71]. The idea behind this simultaneous approach is that combined peripheral sensorimotor activities (which also provide increased sensory feedback) and central brain stimulation (which has the ability to increase or decrease excitability) can enhance synaptic plasticity and motor skill acquisition/consolidation by increasing or modulating afferent inputs to the cortex at a time when it is receiving central stimulation. Cortical stimulation studies in experimental stroke models have shown beneficial effects of combining peripheral activities with central stimulation. Furthermore, studies have shown that paired associative brain stimulation and repetitive median nerve stimulation at the arm raised motor cortical excitability to a level higher than that produced by cortical stimulation alone [74]. This increase was not seen when the same procedure was performed under the influence of dextromethorphan, which is known to block LTP [75].

Motor skill learning has been shown to produce LTP and LTD changes in the primary motor cortex in animal studies [76]. It seems possible that combining repetitive peripheral stimulation or rehabilitative therapy along with transcranial brain stimulation through tDCS in subacute or chronic stroke patients can potentiate relearning and consolidation of motor skills to a level unattainable by any of these interventions alone.

Limitations of tDCS

The mechanisms and neural correlates underlying tDCS have not been explored fully. Further experimental animal, neurophysiological and imaging studies are necessary to better understand the mechanisms and neural correlates of tDCS. The optimal post-stroke time-point at which tDCS should be administered to enhance the chances of recovery has not yet been established. Results of initial studies have focused mainly on the chronic stroke time period in outpatient settings. Future studies should examine the effects of tDCS in subacute settings and possibly compare subacute interventions with chronic interventions to determine the optimal timepoint or timepoints for a tDCS-based intervention. Furthermore, with the introduction of multisession tDCS studies, it is important to establish safety guidelines and set parameters for monitoring treatment effects, dose effects and the early detection of adverse effects. tDCS is poorly localized and might not be ideal for interventions requiring precise localization; it may even lead to interference by either stimulating or depressing perilesional areas, which could increase variability in results. The behavioral and neural effects of different electrode montages (i.e., location of active and reference electrodes) needs to be examined in a more systematic way. Similarly, a more systematic examination is needed into whether both hemispheres respond similarly to tDCS or whether there are hemispheric differences depending on which hemisphere is dominant for a

particular task [77,78]. Interindividual differences in conductivity or resistance due to hair, scalp and bone composition need to be taken into consideration, since they may have an effect on how much current is injected into the brain.

Expert commentary

In conclusion, tDCS is a portable, safe, noninvasive brain stimulation technique that 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 observed if the behavior tested draws on the region that is stimulated. tDCS has enormous clinical potential for use in stroke recovery because of its ease of use, noninvasiveness, safety (does not provoke seizures), sham mode (important for controlled clinical trials) and the possibility of combining it with other stimulation/stroke recovery-enhancing methods (e.g., simultaneous occupational/physical therapy). If the results of pilot and proof-of-principle studies showing long-lasting benefits can be replicated, tDCS might become a very important adjuvant therapy in routine rehabilitative procedures in both acute and chronic stroke settings.

Figure 4. Diffusion tensor imaging in stroke recovery. This picture shows two patients with their representative pyramidal tract fibers that originate from the white matter underlying the precentral gyrus and travel through the internal capsule into the brainstem. The lesional hemispheres show a difference between both patients. **(A)** One patient shows a reduced number of fibers that descend and go through the internal capsule into the brainstem while **(B)** the other patient does not have fibers that originate from the hand/arm region of the precentral gyrus, although some fibers seem to descend through the internal capsule. The stroke lesion in this patient has disrupted the pyramidal fiber bundle. The improvement after transcranial direct current stimulation in combination with occupational therapy was pronounced in the patient with intact pyramidal tract but only minimal in the patient with the disrupted pyramidal tract.

Five-year view

Future studies will examine the underlying molecular, neurophysiological and imaging correlates of tDCS in more detail. This information will then be used to refine the intervention with regard to current strength, current duration, polarity applied and possible combination with other peripheral stimulation techniques or neuromodulatory substances.
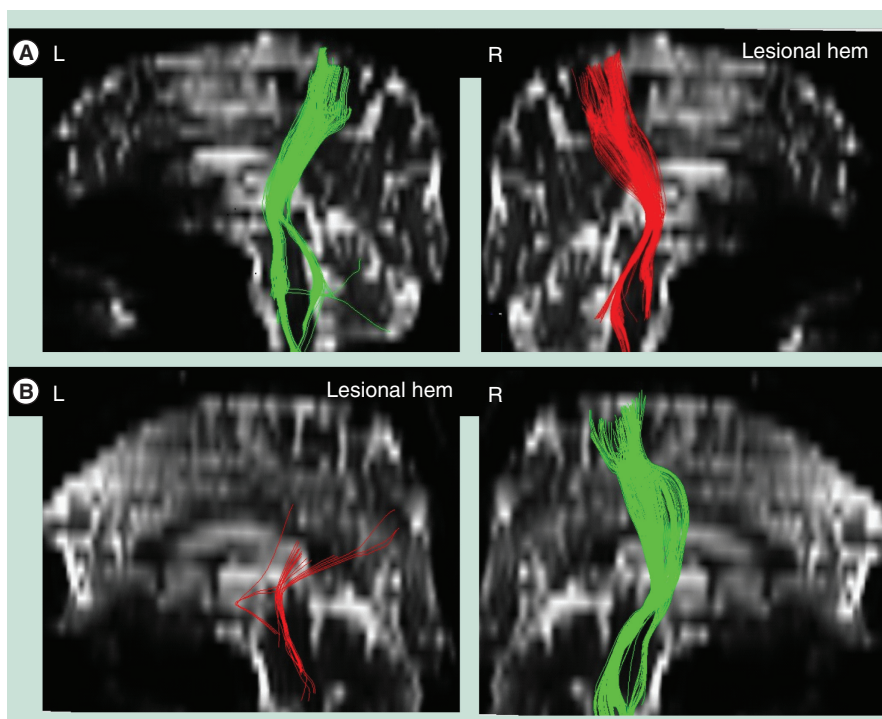
Combination of tDCS with pharmacotherapy is a very promising avenue to pursue and is likely to lead to additive effects. There is already some evidence that the after effects of tDCS can be enhanced or prolonged with certain neuromodulatory substances.

Future studies will also focus more on the acute and subacute stroke phase and make use of excitability changes in the perilesional and contralesional cortex to enhance sensorimotor and cognitive recovery.

Key issues

- Noninvasive brain stimulation using transcranial direct current stimulation (tDCS) is fast re-emerging as an interventional tool to modulate the effects, and possibly treat the symptoms, of several neurological and psychiatric disorders.
- Noninvasive brain stimulation plays an important role in stroke rehabilitation both by stimulating the affected perilesional cortex and the intact, contralesional hemisphere to achieve a balanced interhemispheric inhibition.
- Experiments with tDCS have shown that modulating regional excitability can have effects on sensorimotor and cognitive tasks if these tasks draw on regions that are affected by the noninvasive brain stimulation. One session of 20–30 min stimulation can lead to behavioral/cognitive effects that may outlast the stimulation by more than 30 min.
- Preliminary results of ongoing studies suggest that repeated sessions and long-term stimulation over several days or weeks in conjunction with physical/occupational rehabilitation might have additive effects and may lead to enhanced recovery effects compared with control interventions, and that these effects may last for days or weeks beyond the end of the stimulation period.

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