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Transcranial Direct Current Stimulation for Poststroke Motor Recovery: Challenges and Opportunities

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Abstract

There has been a renewed research interest in transcranial direct current stimulation (tDCS) as an adjunctive tool for poststroke motor recovery as it has a neuro-modulatory effect on the human cortex. However, there are barriers towards its successful application in motor recovery as several scientific issues remain unresolved, including device-related issues (ie, dose-response relationship, safety and tolerability concerns, interhemispheric imbalance model, and choice of montage) and clinical trial-related issues (ie, patient selection, timing of study, and choice of outcomes). This narrative review examines and discusses the existing challenges in using tDCS as a brain modulation tool in facilitating recovery after stroke. Potential solutions pertinent to using tDCS with the goal of harnessing the brains plasticity are proposed.

Introduction

Motor deficit is the most common physical complication after stroke, and improving motor outcomes remains a challenging issue in the field of stroke recovery. Dynamic changes in motor cortical excitability across the lesional hemisphere (decreased cortical excitability) and the contralesional hemisphere (overactivated cortical excitability) after stroke have been observed [1]. This interhemispheric imbalance or inhibition has been the model for several proposed experimental brain modulation tools. Transcranial direct current stimulation (tDCS) can modulate cortical excitability (a typical configuration involves an anodal electrode on the lesional hemisphere and a cathodal electrode on the contralesional hemisphere) with a lasting after-effect in a somewhat dose-dependent fashion [2]. tDCS may improve motor skill learning through augmentation of synaptic plasticity that requires brain-derived neurotrophic factor secretion and Tyrosine receptor kinase B activation [3].

Several tDCS studies in poststroke motor recovery, either a single session or multiple sessions, have examined potential benefits as well as safety profiles [4-7]. The relatively low cost and the ease of administering tDCS has boosted this flurry of studies. However, data on tDCS efficacy in stroke motor recovery have been mixed and inconsistent, leaving several issues to be resolved before tDCS is ready for widespread clinical application in poststroke motor recovery.

In this review, we will systematically examine and discuss the hurdles and challenges in using tDCS as a brain modulation tool to enhance and facilitate recovery after stroke and propose potential solutions pertinent to using tDCS with the goal of harnessing these opportunities.

Interhemispheric Inhibition Model and Montage

An influential theoretical model upon which much of noninvasive brain stimulation for stroke patients is based includes the following: (1) an interhemispheric inhibition of human motor cortex (ie, each motor cortex inhibits the other one); and (2) the imbalance of such interhemispheric motor interactions after a stroke with the unaffected and overexcited motor cortex exerting an unmatched transcallosal inhibitory effect onto the affected motor cortex, which in turn interferes with the recovery process [8,9]. Therefore, the approach for applying tDCS generally has been to either up-regulate the lesional hemisphere with excitatory anodal stimulation, down-regulate the contralesional hemisphere with inhibitory cathodal stimulation, or use bihemispheric stimulation by applying anodal stimulation on

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the lesional side and cathodal stimulation on the contralesional side simultaneously [4].

There have been several challenges to this conventional wisdom. For example, a recent study of transcranial magnetic stimulation (TMS) revealed corticomotor excitability did not change for the contralesional hemisphere during a period of motor recovery, thus challenging the notion that cathodal stimulation applied to the contralesional side is necessary [10]. A subsequent meta-analysis of 112 published studies using TMS showed that the neurophysiological effects of stroke are mainly localized to the lesioned hemisphere, and there was no clear evidence for hyperexcitability of the contralesional hemisphere or interhemispheric imbalance after stroke [11]. One study on tDCS demonstrated that cathodal stimulation on the ipsilesional hemisphere during the subacute phase of stroke could improve motor function as well as reduce spasticity [12]. Recently, Waters et al [13] also challenged this interhemispheric inhibition model, in which they proposed that the 2 hemispheres interact cooperatively rather than competitively. Regardless, their experiment supported the notion that bihemispheric stimulation (using either montage) yielded substantial performance gains relative to unihemispheric (anodal or cathodal) or sham stimulation. Therefore, it is not clear whether the interhemispheric inhibition model still holds for patients with stroke with unihemispheric infarcts and possibly altered interhemispheric interactions.

Different montages may generate different electric fields and may have differential brain modulatory effects [14,15]. For example, extracephalic montages may lead to the significantly greater amount of currents passing through the brainstem when compared with other montages where both electrodes are positioned on the scalp. Extracephalic montages are no longer used in patients with stroke due to this safety concern, but it may deserve further investigation. Three common electrode montages used in poststroke motor recovery are: (1) anodal montage (anode on ipsilesional C3/4, cathode over the supraorbital region on the contralesional hemisphere, eg, FP2/1 in 10/20 electroencephalography system); (2) cathodal montage (anode on ipsilesional FP1/2, cathode on contralesional C4/3); and (3) bihemispheric montage (C3/C4 montage with anode on the ipsilesional motor cortex and cathode on contralesional motor cortex). Theoretically, the bihemispheric montage may offer an advantage of simultaneous excitation of the hypoactive ipsilesional motor cortex and suppression of contralesional motor cortex [8,9,16]. Two studies in healthy subjects showed stronger motor learning effects after bihemispheric stimulation than after unihemispheric stimulation [16,17]. A recent meta-analysis of tDCS poststroke motor studies demonstrated that bihemispheric montage might have better odds of success than unihemispheric montages either with cathodal on the contralesional or anodal on the lesional side montage regarding reducing motor impairment as measured by the Fugl–Meyer Motor Scale [18].

Optimal Dose and Safety Concerns

Hundreds of studies on tDCS have been performed in healthy control subjects as well as subjects with various disease conditions, including stroke. However, the optimal tDCS dose, with maximal efficacy and safety, has not been well established in humans, especially in patients with stroke. Early data suggested that there is a dose–response relationship from 0.1 mA to 1 mA using an amplitude of motor-evoked potentials (MEPs) as a surrogate measure of cortical excitability in healthy subjects [19]. More recently, a positive dose-dependent relationship between the upper extremity motor impairment reduction and current density in the 0.03-0.09 mA/cm^2 range (not current level) was demonstrated in a meta-regression using data from patients with stroke [18]. It is not clear whether this trend will extend beyond this dose range. Two proof-of-concept studies showed signs of promise. Greater current strengths led to greater cortical excitability in otherwise-identical tDCS stimulation setup [20]. The use of smaller pad sizes while controlling for tDCS current amplitudes and other stimulation parameters (leading to greater current density) also led to greater cortical excitability [21].

The primary concern of greater doses of tDCS is centered on potential injury to the brain, but a study in animals suggested that up to 2 orders of magnitude greater doses, ie, 14.29 mA/cm^2, than the ones used in human protocols are required before any structural brain injury occurs [22]. For example, tDCS at 10 mA with 35-cm^2 pad size for 30 minutes translates to a current density of 0.286 mA/cm^2 at the skin–electrode interface with the charge density of 5143 C/m^2, which is an order of magnitude lower than the doses (charge density between 52400 to 72000 C/m^2) that caused brain injury in rodents (Figure 1). Charge density is a more comprehensive safety

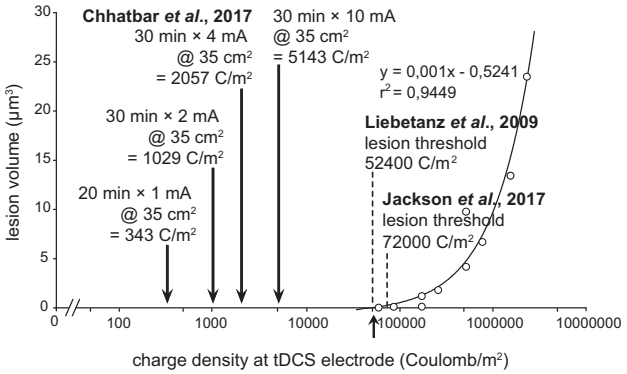

Figure 1. Comparison of safety between animal and human studies based on tDCS dose levels. Typical human studies involve charge density (current amplitude × duration of stimulation ÷ pad size) of ~1 kC/m^2 or less. A recent tDCS dose-escalation study demonstrated the safety of ~2 kC/m^2 in subjects with stroke. Stimulation using 10 mA tDCS for 30 minutes on a standard 35-cm^2 pad size offers ~5 kC/m^2 charge density, which is still an order of magnitude lower than >50 kC/m^2 as required in animal studies to cause brain injury. tDCS, transcranial direct current stimulation.