

Perspective for Clinical Application and Research of Transcranial Direct Current Stimulation in Physical Therapy



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Neurostimulation approaches have been developed and explored to modulate neuroplastic changes of cortical function in human brain. As one of the most primary noninvasive tools, transcranial direct current stimulation (tDCS) was extensively studied in the field of neuroscience. The alternation of cortical neurons depending on the polarity of the tDCS has been used for improving cognitive processing including working memory, learning, and language in normal individuals, as well as in patients with neurological or psychiatric diseases. In addition, tDCS has great advantages: it is a non-invasive, painless, safe, and cost-effective approach to enhance brain function in normal subjects and patients with neurological disorders. Numerous previous studies have confirmed the efficacy of tDCS. However, tDCS has not been considered for clinical applications and research in the field of physical therapy. Therefore, this review will focus on the general principles of tDCS and its related application parameters, and provide consideration of motor behavioral research and clinical applications in physical therapy.

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I. Introduction

Excitability of cortical neurons can be modulated by invasive or non-invasive techniques in human brain.¹⁻⁵ The study of changes in brain function by external stimulation is an important issue in neurological and physical therapy because of the potential for scientific interventions. Recently, numerous investigations revealed that changes in motor function can be induced by electrical stimulation of cortical neurons in invasive or non-invasive manners. As representative invasive techniques, implanted cortical stimulation has been generally used in therapeutic applications for brain tumors or epilepsy surgery, with epidural or subdural placement. Epidural implantation has better clinical effects compared to subdural stimulation, in terms of increased activation threshold and reduced risk of seizure.⁶ Previous studies indicated that a cathode excites preferentially the fibers that run horizontally under the motor cortex, whereas an anode excites the fibers that are perpendicular to the surface.⁷ On the other hand, non-invasive techniques have been extensively investigated for modulating brain function, because

of the great advantages of easy, repetitive application and no tissue damage.⁸⁻¹⁰

As one of the most primary noninvasive tools, transcranial direct current stimulation (tDCS) and transcranial magnetic stimulation (TMS) have been extensively studied in the field of neuroscience.¹¹⁻¹³ In particular, a constant direct current that can polarize tissues by the flow of electric charge, is known to easily change the excitability of human nerves through the skin, and even stimulate the vestibular system through the skull. tDCS is a recently re-introduced technique for stimulating cortical neurons by delivery of weak currents through the skull, which leads to changes in polarity-dependent excitability.^{4,14} For example, the excitability of cortical neurons is increased by anodal tDCS, whereas it is decreased by cathodal tDCS. Alternation of cortical neurons depends on the polarity of tDCS and have been used for improving cognitive processing including working memory, learning, and language in normal individuals, as well as in patients with neurological or psychiatric diseases.¹⁵⁻¹⁹ Numerous previous studies have confirmed the efficacy of tDCS.

tDCS has the ability to modulate brain function and induce behavioral changes, depending on the parameters of stimulation, in terms of intensity, duration, and location. In addition, tDCS has been associated with improvement of motor function in motor learning and working memory in normal subjects¹⁹ as well as in stroke patients.¹⁹⁻²¹ In particular, application of tDCS to the motor cortex has the potential to enhance functional motor performance.^{14,22-25} According to prior tDCS studies,^{14,22,26} tDCS can not only facilitate strength and increase fatigue resistance of the targeted muscle, but also reinforce higher motor function such as visuo-motor coordination. Those behavioral results are described for ongoing or long lasting tDCS effects.^{12,16,18,24} In addition, functional neuroimaging studies using functional MRI (fMRI), positron emission tomography (PET), and TMS have revealed that cortical excitability of the motor cortex is induced or increased during or after delivery of tDCS.²⁷⁻²⁹

As mentioned above, numerous studies have reported effects of tDCS on neurophysiologic and behavioral functions in normal individuals and in patients with neurological and psychiatric disorders.^{3,20,28-30} However, in the field of physical therapy, only a few studies have reported evidence of enhanced motor and cognitive function. Therefore, this review will focus on the general principles of tDCS and its related application parameters, and consider motor behavioral research and clinical applications in physical therapy.

II. Electrical parameters of tDCS application

Safety guideline is an important issue because of the application of a weak direct current through electrodes on the scalp. In general, all studies concerning safety have indicated that no adverse effects occur if one applies a current with an intensity of 1 mA for up to 20 min using electrodes whose area is about 25~35 cm.^{28,10,31} So, tDCS has extensively been used in many neurophysiologic and clinical trials because of its safety and easy application. A protocol of tDCS application is composed of current strength, electrode size, and stimulation duration. The current density at the targeted brain area is a basic element for effective electrical stimulation beneath cortical neurons. tDCS has to modify spontaneous neuronal excitability of neural tissue by a depolarization or a hyperpolarization of the resting mem-

brane potential.^{32,33} The ability of tDCS to modulate membrane potential depends on current density, which determines the electrical field strength through critical factors such as current strength and electrode size.³² Nitsche et al³⁴ suggested that a reduction in electrode area can increase the focality of tDCS, and that an increase in electrode area can cause the procedure to become functionally ineffective. Direct currents have generally been delivered through a pair of sponge electrodes moistened with water or NaCl solution.^{4,5,8,20} Electrodes that do not induce electrochemical effects such as electrolysis are recommended. Wet skin might be helpful to reduce electrical resistance and improve the homogeneity of the electric field under the electrodes, which minimizes patient discomfort.

Studies have used current densities that ranged from 0.03 to 0.08 mA/cm².³ In an animal study by Yuen et al in 1981,³⁵ direct current stimulation of the cerebral cortex in cat induced histological damage in the range of 40~400 mC/cm² per phase. However, in a study by Agnew and McCreery,³⁶ electrical stimulation with 40 mC/cm² was proposed, for safety reasons, as a maximum charge density at the stimulating electrode. Generally, direct current stimulation at 1 mA intensity with an electrode area of 35 cm² has been used for several minutes, based on the safety limits proposed by Nitsche and Paulus.^{4,37} For increasing focality of tDCS, reduced electrode size, maintenance of a constant current density, and an extracephalic reference have been considered. Nitsche et al³⁴ indicated that the excitability of primary motor cortex could be changed effectively by tDCS with a 3.5 cm² electrode keeping current density constant. They suggested that the small electrode resulted in a more spatially limited excitability modification, compared to a large 35 cm² electrode. Corticospinal excitability of the motor cortex can be modulated by a smaller electrode, the effect of which was similar to a larger one, but the effects of a smaller electrode on intracortical inhibition and facilitation were abolished and the variability of the effects was larger.¹² Most participants felt a slight itching sensation during the initial phase of stimulation, which then faded in most cases. When delivery of direct current is started and when the reference electrode is not located on the head, other sensations can occur in the area of the other electrode. These effects can be avoided by ramping current up and down at the beginning and end of stimulation.

As another important parameter of tDCS, electrode positions are considered. The anode is the positively charged

electrode, and the cathode is the negatively charged electrode. Electrical current flows from the cathode to the anode. A variety of electrode position combinations were investigated for modulating neural excitability and function of motor cortex in human brain. Effective combinations can be used for modulation of different neuronal populations.^{4,5} In general, an active electrode is placed on the targeted cortical areas where neural function is modulated; the other electrode is attached to the contralateral supraorbital area, vertex, neck, or deltoid muscle. Nitsche et al³ suggested that tDCS protocols should specify electrode position as accurately as possible, because different current flow directions may result in different effects. Moreover, current direction and electrode position can affect the amount of shunting, and thereby alter the amount of current delivered to brain tissue.³ In conclusion, no side effects induced by direct current stimulation have been reported in most tDCS studies, and the criterion for maximum stimulation has not yet been established.

The efficacy of tDCS depends on the stimulus duration. If all other parameters are held constant, an increase in the stimulation duration results in longer-lasting and stronger effects.^{4,38} In most studies, various stimulation durations have been used (from several minutes to 20 minutes) according to the goal of the given study. A short stimulation duration of anodal or cathodal tDCS increases neural excitability during stimulation, but no after-effects were induced. For human motor cortex, tDCS applications for several minutes led to lasting after-effects.⁴ Several investigations revealed that application durations of 9~13 min resulted in being stable for up to an hour.^{37,38} Determination of the optimal stimulation duration for eliciting maximal tDCS effects will continue to be an important issue in clinical and research settings. However, such proof would depend on the targeted cortical area. Therefore, further studies to explore optimal stimulation durations are needed.

III. Evidence of tDCS for motor system modulation

Numerous tDCS studies demonstrated that direct current modulates cortical neurons under the scalp,^{3,5,8,21,30} using transcranial magnetic stimulation (TMS). TMS is a noninvasive method for causing depolarization of neurons, and can be used clinically to measure activity and function of specific brain

circuits in humans. In addition, cortico-spinal excitability of the primary motor cortex was measured by determining active and resting motor thresholds using a single TMS test-pulse.^{39,40} According to Nitsche and Paulus,⁴ it is possible to selectively increase or decrease cortical excitability by stimulation using weak anodal and cathodal electrical currents; these effects lasted for several minutes after termination of stimulation. In a recent study, Lang et al²⁹ reported that 10 minutes of tDCS of the primary motor cortex can facilitate or suppress MEPs evoked from the same hemisphere, depending on the polarities. Such effects lasted at least 40 minutes after stimulation. Along with these effects on MEPs, the duration of transcallosal inhibition evoked from the right primary motor cortex was prolonged after anodal and shortened after cathodal tDCS. They proposed that tDCS has a prolonged action on the excitability of the synaptic connections that these two populations of neurons make with corticospinal cells; anodal tDCS increases the effectiveness of both sets of synapses, whereas cathodal tDCS decreases their effectiveness. In addition to studies regarding modulation of cortical neurons in the hand motor area, whether changes in the excitability of deeper cortical structures could be induced by tDCS has recently been explored. Jeffery et al. studied whether direct current of 2 mA could have an effect on similar changes in the excitability of deeper cortical structures that innervate muscles of the lower leg. Ten min of anodal tDCS on the leg area in the motor cortex enhanced the excitability of corticospinal tract projections to the tibialis anterior muscle; this was seen as an increase in the amplitude of the motor evoked potentials evoked by TMS. They suggested that it is more difficult to suppress the excitability of the leg motor cortex with cathodal tDCS than the hand area of the motor cortex. Excitability changes in the interconnected cortical areas at a distance from the stimulation point were modulated. Boros et al¹² revealed that tDCS of the premotor area selectively influences intracortical excitability of the ipsilateral primary motor cortex. It is well known that the premotor area is densely interconnected to other motor related cortical areas. They found that anodal tDCS significantly reduced intracortical inhibition, and enhanced intracortical facilitation.

On the other hand, neuroimaging studies to induce cortical activation by tDCS were published. Kwon et al²⁸ demonstrated that tDCS has a direct stimulating effect on the underlying cortex. They applied a constant current with an intensity of 1.0

mA to the scalp over the central knob of the M1 in the left hemisphere in eleven right-handed healthy subjects. Their findings showed that the central knob of the left primary motor cortex was activated, and the left supplementary motor cortex and the right posterior parietal cortex were also activated. In a follow up fMRI study, Kwon et al⁴¹ demonstrated that ongoing effects of tDCS were induced after 1 minute since the direct current is applied to the target neurons, and such effects were maintained during a lasting tDCS. Nine healthy right-handed subjects were scanned for five consecutive phases (control-tDCS1-tDCS2-tDCS3-tDCS4) during a total of five minutes, with even duration (1 minute) in each phase, while tDCS at 1.0 mA was delivered to the hand knob of the precentral gyrus during the four tDCS phases. Therefore, continuing effects of tDCS are induced and maintained after the direct current to the target neurons is turned off.

Several explanations for these effects have been presented. Bindman et al⁴² suggested that the effects are probably due to shifts in neural resting membrane potential, as shown in animal experiments, and the long-lasting effects may be induced by changes in the spontaneous discharge rate of the stimulated neurons. Such a phenomenon is similar to post-tetanic potentiation or short-term potentiation of anodal stimulation, as suggested by Samii et al.⁴³ However, it remains unclear whether the after-effects trigger the biochemical activation of these processes.

IV. Enhancement of motor function by tDCS

Many previous studies demonstrated that tDCS can provide neural cells with sufficient current flow to modulate brain activity and behavior.^{12,21,28,30,44-47} Cogiமானian et al²² suggested that anodal tDCS of the cerebral motor cortex improved isometric force endurance of the elbow flexors. The authors evaluated the maximum voluntary contraction (MVC) for the left elbow flexors and a fatiguing isometric contraction (35% of MVC), before and after brain polarization in 24 healthy subjects. They found that anodal tDCS over the cortical motor areas induced a relative increase in the endurance time of the flexor muscles for a sustained submaximal isometric contraction, and that the duration of residual tiredness was reduced after anodal tDCS up to 15%, compared to cathodal tDCS and no

stimulation. Therefore, the author concluded that brain polarization by tDCS can modulate neuromuscular fatigue, and suggested the possibility of improving muscle performance and decreasing muscle fatigue in normal and pathological conditions. According to Boggio et al's study in 2006,¹³ tDCS over the non-dominant motor cortex could increase its excitability. Their main finding of our study was that motor performance of the non-dominant hand significantly increased after stimulation, as documented by the Jebsen Taylor Hand Function Test. In addition, it was shown that motor performance of the legs as well as of the hands could be improved by anodal tDCS.

Several recent studies suggested that motor skill learning can be enhanced by the after-effects of tDCS on cerebral cortex related motor function.^{16,24,48,49} According to Antal et al's study,⁴⁸ after 10 minutes of tDCS of the primary motor cortex or the visual area MT/V5 in healthy subjects, the accuracy of tracking tasks increased significantly in the early phase of practice after both anodal and cathodal stimulations over both cortical areas, compared to the no-stimulation condition, which showed a behavioral improvement at the beginning of the practice process. In addition, Hunter et al²⁴ investigated whether anodal tDCS could augment the development of a novel internal model of motor control when applied to the PMC during force field-induced motor adaptation. They found that active tDCS induced a significantly greater global reaching (overshoot) error during the early stage of de-adaptation and initial movement trajectory (signed error in the first 150 ms of movement), compared to the sham tDCS condition through arm-reaching movement trials. Finally, the authors suggested that anodal tDCS augments the development of an internal model of the novel adapted movement, and suggests that the primary motor cortex is involved in adaptation of reaching movements of healthy human subjects. Along with after-tDCS effects on motor learning experiment, studies that the excitability of the cortical neurons was modulated by the ongoing effect during delivery of tDCS,^{28,41} were published.^{17,27} Dockery et al¹⁶ examined whether motor planning ability could be improved during tDCS application using 1 mA for 15 minutes on the left dorsolateral prefrontal cortex in 24 healthy subjects. The authors found that motor performance of the Tower of London task was enhanced during acquisition and early consolidation. Also, Stone et al¹⁵ revealed that tDCS on the

left parietal cortex modulated the performance of local-to-global attentional switching by the ongoing effect of tDCS. Previous TMS studies showed that the motor cortex is characterized by having a lower motor threshold, a higher motor evoked potential, and a shorter silent period, after acquisition of motor skilled learning. Accordingly, the activities of cortical neurons and brain functions can be modulated during delivery of direct current, and these changes can be attributed to the ongoing effects of tDCS. Also, tDCS could represent an effective means to increase the excitability of the motor cortex and thus enhance motor performance. We speculate that tDCS may become an important alternative therapy for motor recovery of stroke patients in the future.

Several neuroimaging studies have demonstrated ongoing and after effect of tDCS, in addition to the two fMRI experiments mentioned above.^{27-29,41,50} To our knowledge, the fMRI study conducted by Baudewig et al in 2001,²⁷ is the first attempt to use neuroimaging to detect tDCS-induced modulations of brain activity by BOLD signal changes. Their findings showed that, after anodal tDCS with 1 mA applied for 5 minutes to the motor cortex area corresponding to hand function, brain activity was slightly increased by the sequential finger opposition task, although the difference was not significant. According to the PET study by Lang et al. in 2005,²⁹ the regional cerebral blood flow in brain areas related to motor function was increased by the sequential finger movement test after anodal tDCS application to the left M1. In a more recent fMRI study published by Jang et al⁵⁰ and Stagg et al⁵¹ in 2009, tDCS applied to the hand motor cortex increased the underlying motor cortex activation caused by a hand motor task in terms of the voxel count and peak intensity. These findings suggest that the excitability of cortical neurons is modulated by ongoing effects as well as after effects of tDCS.

V. tDCS for clinical application

Based on these experiments in normal subjects, several clinical studies have tried to determine whether the application of tDCS improves motor function of their paretic limbs in stroke patients.^{19,46,52} According to the double blind crossover study by Hummel et al and Fregni,^{19,20} tDCS applied to the motor cortex of the affected hemisphere resulted in functional improvement

in the paretic hand of chronic stroke patients, an effect that outlasted the stimulation period, as measured by the Jebsen Taylor Hand Function Test. In addition, Bolognini et al⁵³ revealed that cathodal tDCS induced a decrease in left motor cortical excitability, which dampened the inhibitory influence of the left motor area on the homologous right motor area, and that this disinhibition of the right hand caused enhanced performance in left-hand sequential finger movements. Moreover, the effects of direct current stimulation combined with a new treatment method were introduced.⁵⁴ Edwards et al⁵⁴ evaluated whether anodal tDCS plus robotic wrist therapy could increase corticomotor excitability in muscles acting at the wrist. The authors measured corticomotor excitability and short-interval cortical inhibition through motor evoked potentials generated by TMS in the flexor carpi radialis, before and immediately after a period of tDCS (1 mA, 20 min, anode, and TMS applied to the lesioned hemisphere), and robotic wrist training (1 hour) in six chronic stroke patients with residual motor deficit. They found that increased corticospinal excitability accompanied by reduced cortical inhibition following anodal tDCS can occur in forearm muscles of chronic stroke patients, and the effect persists during task-specific robotic wrist training. Accordingly, tDCS was shown to improve motor and cognitive functions in patients with stroke, and its clinical efficiency was well established.^{3,17,19,20,23,25} We believe that tDCS has a great clinical advantage as an adjuvant treatment tool, when concurrently used with conventional interventions or robotic assisted therapy. The prior findings produce the evidence to facilitate the underlying brain function by tDCS application in company with motor performance. Further studies are expected to demonstrate the clinical effects of tDCS as an adjuvant treatment tool in patients with stroke when it is concurrently administered with conventional interventions to improve brain function after a stroke.

VI. Conclusion

Transcranial application of weak direct currents is an effective approach for changing neuronal activity and behavior. tDCS has been re-evaluated as a non-invasive intervention tool. However, tDCS has not been considered for clinical applications or even research in the field of physical therapy. Therefore, we expect

that the current study will provide physical therapists with a much needed perspective for considering clinical and research applications of transcranial direct current stimulation.

Author Contributions

Research design: Kim CS

Acquisition of data: Nam SH

Analysis and interpretation of data: Nam SH

Drafting of the manuscript: Kim CS, Nam SH

Research supervision: Kim CS

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