Special Article

Basic Knowledge of Transcranial Direct Current Stimulation

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Background: *Transcranial direct current stimulation (tDCS) was a neurophysiologic technique using weak electrical currents (1-2 mA) to modulate the activity of neurons in the brain. It was discovered in the 1960s, and then reintroduced by the reasonably well-controlled experiments 12 years ago. They suggested that electrodes placed on the head can produce noticeable neurological changes depended on the current direction.*
Objective: *To review a basic technique of the instrument, mechanism of action, and application in clinical researches of tDCS.*
Material and Method: *The tDCS studies were thoroughly reviewed in MEDLINE database using the key words "Transcranial direct current stimulation, tDCS, noninvasive brain stimulation, neurophysiologic technique" from 1998 to 2010.*
Results: *The basic technique of the instrument, mechanism of action, application in clinical researches such as stroke, pain syndrome and craving; safety, side effect, and precaution of tDCS are described.*
Conclusion: *tDCS study is rapidly increasing and accepted as a noninvasive technique. It is easy to use and safe. The outcomes of tDCS in clinical researches are preferable with very little side effects.*

Keywords: *Transcranial direct current stimulation, tDCS, Noninvasive brain stimulation, Neurophysiologic technique*

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Transcranial direct current stimulation (tDCS) is the application of weak electrical currents (1-2 mA) to modulate the activity of neurons in the brain[1,2]. It was first described 50 years ago in animal studies and reintroduced as a non-invasive brain stimulation technique to alter cortical activity in human 12 years ago[3-5].

Studies combining tDCS with functional magnetic resonance tomography, positron emission tomography and electroencephalography promise to provide invaluable insights on the correlation between modifications of behavior[2]. In addition, tDCS is useful in clinical treatment in stroke, migraine, pain syndrome, and craving.

The aim of this article is to propose guidelines on how to perform tDCS safely and effectively. Because many laboratories have just started using this technique, it is necessary to stratify stimulation protocols to enhance comparability of research results. So we describe about the instrument and mechanism of action, the application of tDCS in clinical researches, safety, side effect and precaution of tDCS.

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The instrument and mechanism of action

There are two essential components in tDCS device, the first is power supply and the second are electrodes[2]. The power supply is nine volts of direct current, which delivers via a pair of surface conductive electrodes[2]. To decreasing the impedance, the electrodes should be covered with saline or gel soaked sponges[2]. The proper size for the electrodes, which are suited for a constant current density and focality, are 25-35 cm^2[2]. The proper current density delivered is between 0.029 and 0.08 mA/cm^2[2].

The anode is defined as the positively charged electrode, whereas the cathode is the negatively charged one[2]. Current flows from the cathode to the anode[2]. The effects that occur at anode and cathode electrodes are different. Anodal stimulation in animal models has shown that it increases excitatory neuronal firing rates while cathodal

decreases them[6]. These results were confirmed in human[7]. Initial studies in humans found that anodal stimulation was suggested to diminish depressive symptom[8], while cathodal stimulation reduced manic symptom[9]. The mechanisms of actions proved that cathodal stimulation decreases the resting membrane potential and therefore, hyperpolarized neurons[10]. Whereas anodal stimulation is located near the cell body or dendrites causes depolarization by increasing resting membrane potentials and spontaneous neuronal discharge rates[10]. In general, studies in human showed that the stimulation electrode is usually the anode and is placed on the target area such as motor (M1), central (C3 or C4), or frontal (F3 or F4) area. The reference electrode is usually placed on an extracephalic area such as contralateral supraorbital area or shoulder[2]. The locations of electrodes placing usually followed the international 10-20 electroencephalographic system as shown in the Fig. 1 and 2.

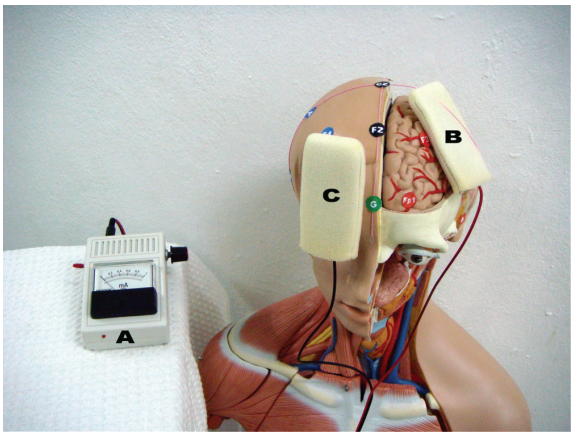

Fig. 1 Transcranial direct current stimulation and 10-20 international electrode placements. A = Nine volts of direct current power supply, B = Stimulation electrode position: M1, motor area between F3 and C3 and C = Reference electrode position on contralateral supraorbital area

Current density of tDCS

The proper current density delivered is between 0.029 and 0.08 mA/cm^2[2]. The higher current density, the longer lasting, stronger and deeper cortical neuron stimulation[4,11,12]. However, it might be painful because of the increasing current density. This will increase cutaneous pain sensation[2].

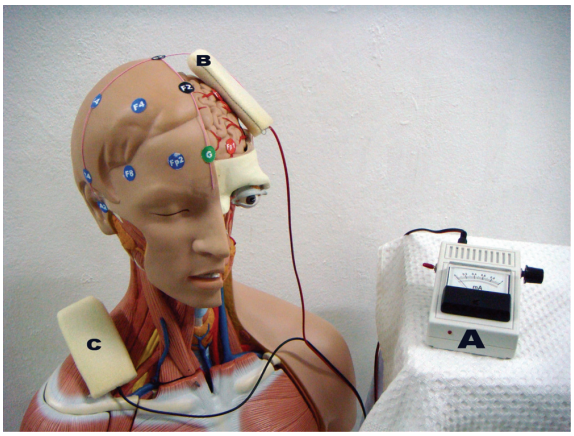

Fig. 2 Transcranial direct current stimulation and 10-20 international electrode placements. A = Nine volts of direct current power supply, B = Stimulation electrode position on M1, motor area between F3 and C3 and C = Reference electrode position on contralateral shoulder.

Direction of the current

tDCS with the anode placed over the primary motor cortex and the cathode over the contralateral orbit causes anterior-posterior direct current flow and increases excitability of motor system (Fig. 1). Whereas the reversed electrodes with the cathode over the primary motor cortex cause a posterior-anterior current flow and reduced excitability[2].

The relationship between the duration of stimulation and the lasting effect

When tDCS was applied for four seconds, it will not elicit after effect[12]. The stimulation duration for 10 minutes caused one hour lasting effect (or we can call short-lasting after effect)[13]. When the stimulation last for one hour or more, it caused 48 hours to one week lasting effect (or we can call long-lasting after effect)[14]. Breaking between the stimulation sessions should be based on lasting effect. Therefore, four seconds of stimulation should have a break for 10 seconds[12], 10 minutes of stimulation, break one hour[13] and one hour stimulation, break one week. This is sufficient[14]. If the aim is to induce more stable changes in cortical function, repeated daily tDCS sessions may be adequate[2].

The application of tDCS in clinical researches

tDCS is also useful in clinical treatment in stroke[5,21-29], pain syndrome[30-36] and craving[37-39] (Table 1). The results of treatment were tentatively favorable but there were still insufficient amount of

Table 1. Summary of tDCS in clinical researches

Topic/authors	Study design	Number of subjects	Polarity	Stimulation electrode position	Reference electrode position	Stimulation duration	Stimulation intensity (mA)	Results	Effective duration	Adverse events
Stroke										
Fregni et al, 2005[21]	RCT, crossover	6	A/C/S	M1	Contralateral orbit	20 min	N/A	- Significant improvement in motor performance	N/A	N/A
Hummel et al, 2005 [5]	RCT, crossover	12	A/S	M1, hand area	Contralateral orbit	20 min	1	- Significantly improved hand function	11.3 ± 4.1 days	No significant differences in fatigue, discomfort, and pain
Hummel et al, 2006 [22]	RCT, crossover	11	A/S	M1 of the affected hemisphere	Contralateral supraorbital	20 min	1	- Significantly shortened reaction times and improved pinch force	Not reported	No significant differences in fatigue, discomfort, and pain.
Boggio et al, 2007[23]	RCT	9	A/C/S	M1 (hand area) of the affected (anodal) or unaffected (cathodal) hemisphere	Contralateral supraorbital area	20 min (4 weekly sessions or 5 consecutive daily sessions)	1	- Significant motor function improvement ($p = 0.009$) - Significant effect with daily sessions ($p < 0.0001$) - No cumulative effect with weekly sessions	2 weeks	Not reported
Hesse et al, 2007[24]	Pilot study, opened label	10	A	C3/C4	Contralateral orbit	7 min	1.5	- Significant arm function improvement in 3 patients - Aphasia improved in 4 patients - Little changed arm function in 7 patients	Not reported	No major adverse events, slight itching in 4, bearable headache in 2 patients

Electrode position refers to the international 10/20 system
M1 = primary motor cortex; S1 = primary somatosensory cortex; DLPFC = dorsolateral prefrontal cortex; Reference electrode = electrode is functionally inefficient
Polarity: A = anodal tDCS, C = cathodal tDCS, S = sham tDCS; DLPFC = dorsolateral prefrontal cortex; N/A = not available

Table 1. (cont.)

Topic/authors	Study design	Number of subjects	Polarity	Stimulation electrode position	Reference electrode position	Stimulation duration	Stimulation intensity (mA)	Results	Effective duration	Adverse events
Stroke										
Monti et al, 2008[25]	RCT	8	A/C/S	Experiment 1: left fronto-temporal areas (Broca's region) Experiment 2: occipital areas (2 cm over the inion)	Right shoulder	10 min	2	- Significant improvement in picture naming after cathodal tDCS ($p = 0.002$) - Anodal tDCS and sham tDCS failed to induce any changes - No significant effect of tDCS over the occipital area	Not reported	Occasional, transient and short-lasting tingling, burning sensations below the electrodes
Jo et al, 2009 [26]	RCT, crossover	10	A/S	Left DLPFC	Right supraorbital	30 min	2	- Significant improvement of recognition accuracy ($p < 0.05$) - Not difference in response time	Not reported	Transient aching or burning sensations in 6, transient skin redness at the electrode contact site in 3 cases; disappeared after a few seconds
Celnik et al, 2009[27]	RCT, crossover	9	A/S	Ipsilesional M1	Contralateral supraorbital	20 min	1	- Combined PNS and tDCS significantly improved the performance of a motor sequence task ($p < 0.05$)	Not reported	Not reported

Electrode position refers to the international 10/20 system
M1 = primary motor cortex; S1 = primary somatosensory cortex; DLPFC = dorsolateral prefrontal cortex; Reference electrode = electrode is functionally inefficient
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Table 1. (cont.)

Topic/authors	Study design	Number of subjects	Polarity	Stimulation electrode position	Reference electrode position	Stimulation duration	Stimulation intensity (mA)	Results	Effective duration	Adverse events
Stroke										
Kang et al, 2009[28]	RCT, crossover	10	A/S	Left DLPFC	N/A	20 min (single session)	2	- Significant improvement in response accuracy ($p < 0.05$)	3 hours	N/A
Baker et al, 2010[29]	RCT	10	A/S	Left frontal cortex depended on fMRI	Right shoulder	20 min (5 days)	1	- Significantly improved naming accuracy ($p < 0.04$)	At least 1 week after treatment	No adverse event
Pain										
Fregni et al, 2006[30]	RCT	17	A/S	M1	Contralateral orbit	20 min (5 days)	2	- Significant pain improvement ($p < 0.05$)	At least 5 days	Mild headache, and itching (similar to sham group)
Fregni et al, 2006[31]	RCT	32	A/S	M1, DLPFC	Contralateral orbit	20 min (5 days)	2	- Significant pain improvement in fibromyalgia ($p < 0.0001$)	3 weeks	Sleepness, itching, and headache (similar to sham group)
Roizen-blatt et al, 2007[32]	RCT	32	A/S	Left M1 or DLPFC	Contralateral supraorbital area	20 min (5 days)	2	- M1 stimulation significantly increased sleep efficiency ($p = 0.004$) and decreased arousal ($p = 0.001$) - DLPFC stimulation significantly decreased in sleep efficiency ($p = 0.02$), increased in rapid eye movement ($p = 0.0002$) and increased in sleep latency ($p = 0.02$)	N/A	N/A

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M1 = primary motor cortex; S1 = primary somatosensory cortex; DLPFC = dorsolateral prefrontal cortex; Reference electrode = electrode is functionally inefficient
Polarity: A = anodal tDCS, C = cathodal tDCS, S = sham tDCS; DLPFC = dorsolateral prefrontal cortex; N/A = not available

Table 1. (cont.)

Topic/authors	Study design	Number of subjects	Polarity	Stimulation electrode position	Reference electrode position	Reference electrode position	Stimulation intensity (mA)	Results	Effective duration	Adverse events
Pain										
Boggio et al, 2009[33]	RCT, crossover	8	A/S	C3/C4	Contralateral supraorbital	30 min (single session)	2	- Significant pain reduction ($p = 0.006$)	N/A	N/A
Fenton et al, 2009[34]	RCT, crossover	7	A/S	M1 dominant hemisphere	N/A	20 min (2 days)	1	- Modest pain reduction in refractory chronic pelvic pain	N/A	N/A
Antal et al, 2010[35]	RCT	23	A/S	Left M1	Contralateral supraorbital	20 min (5 days)	1	- Significant pain improvement ($p < 0.05$)	At least 28 days	Light headache (similar to sham group)
Mori et al, 2010[36]	RCT	19	A/S	C3/C4 contralateral to somatic painful area	Supraorbital contralateral to stimulated motor cortex	20 min (5 days)	2	- Significant pain improvement ($p < 0.05$)	At least 28 days	No adverse event
Craving										
Boggio et al, 2007[37]	RCT	13	A/C/S	F3/F4	Homologue area Cathodal electrode of 100 cm^2	20 min	2	- Both anodal left/ cathodal right and anodal right/ cathodal left significantly decreased alcohol craving compared to sham stimulation ($p < 0.0001$)	Not reported	Discomfort, headache, mood changes, and itching (similar to sham group)
Fregni et al, 2007[38]	RCT, cross over	23	A/C/S	F3/F4	F4/F3	20 min	2	- Craving was significantly reduced only after anode right/cathode left stimulation (reduction by 17.9%, $p = 0.0034$)	Not reported	Few mild adverse events (similar to sham group)

Electrode position refers to the international 10/20 system
M1 = primary motor cortex; S1 = primary somatosensory cortex; DLPFC = dorsolateral prefrontal cortex; Reference electrode = electrode is functionally inefficient
Polarity: A = anodal tDCS, C = cathodal tDCS, S = sham tDCS; DLPFC = dorsolateral prefrontal cortex; N/A = not available

Table 1. (cont.)

Topic/authors	Study design	Number of subjects	Polarity	Stimulation electrode position	Reference electrode position	Reference electrode position	Stimulation intensity (mA)	Results	Effective duration	Adverse events
Craving										
Boggio et al, 2009[39]	RCT	27	A/S	F3	F4	20 min (5 days)	2	- Both left and right DLPFC tDCS, reduced smoking craving after cue-exposition	Not reported	Drowsiness, itching, headache, scalp burning, concentration problems, mood changes, tingling (similar to sham group)

Electrode position refers to the international 10/20 system
M1 = primary motor cortex; S1 = primary somatosensory cortex; DLPFC = dorsolateral prefrontal cortex; Reference electrode = electrode is functionally inefficient
Polarity: A = anodal tDCS, C = cathodal tDCS, S = sham tDCS; DLPFC = dorsolateral prefrontal cortex; N/A = not available

studies and number of subjects in each study. Furthermore, the mechanisms of actions of tDCS in each disease are still unknown. Therefore, further studies in clinical and basic neuroscience are needed.

The safety and side effect of tDCS

There have been no serious adverse events with tDCS. The studies used tDCS current density up to 0.029 mA/cm^2 and the stimulation duration up to 13 minutes. Those did not cause heating effects under the electrode[4]. In addition, it also did not elevate serum neuronal specific enolase level[11,12], a sensitive marker of neuronal damage[15]. Additionally, there was no changes of EEG activity, or cognitive distortion[16]. Because tDCS neither causes epileptic seizures nor reduces the seizure threshold in animals[17], seizures do not appear to be a risk for healthy subjects[2]. The studies were tested in more than 3,000 subjects in laboratories worldwide. They did not show serious side effect except for a slight itching under the electrodes, and seldom-occurring headache, fatigue and nausea[10]. Skin irritation appears sometime under the electrodes in some patients, when the treatment is repeated daily with a current density about 0.06 mA/cm^2[2]. Tissue damage might be occuring in a small electrode[18].

Precaution

tDCS should be considered for brainstem or heart nerve stimulation, while delivering current to healthy subjects via bifrontal electrodes. One case had respiratory and motor paralysis with cramping of the hands, accompanied by nausea after treatment. There was no loss of consciousness, and respiration returned when the current was stopped. The subject was not hospitalized, but had impaired fine motor control lasting for two days and eventually returned to normal[19]. The current flow might be focused in skull defect, foramen, open fontanels, or fissures[2]. Subjects should be free of unstable medication, metallic implants near the electrodes and electrodes above mastoids because they stimulate the vestibular system and might induce nausea[20].

Conclusion

Transcranial direct current stimulation was reintroduced 12 years ago. It is an effective and non-invasive tool for studying basic science and therapeutic uses. There were reports of the therapeutic outcomes in stroke, pain syndrome, and craving. However, it is also important to underscore that tDCS research is in

its early stages and therefore the further studies might change some of the current concepts.

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Potential conflicts of interest

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ความรู้พื้นฐานการกระตุ้นด้วยไฟฟ้ากระแสตรงผ่านกะโหลกศีรษะ

ภารดี เอื้อวิชญาแพทย์, ณรงค์ เอื้อวิชญาแพทย์

***ภูมิหลัง**: การกระตุ้นด้วยไฟฟ้ากระแสตรงผ่านกะโหลกศีรษะ เป็นเทคนิคทางประสาทสรีรวิทยาที่ใช้กระแสไฟฟ้าอย่างอ่อน (1-2 มิลลิแอมแปร์) เพื่อปรับเปลี่ยนกิจกรรมของเซลล์ประสาทในสมอง เทคนิคนี้ค้นพบครั้งแรกในราวปี พ.ศ. 2503 และได้นำเทคนิคนี้มาเสนอใหม่ โดยการทดลองที่มีเหตุผลและมีการควบคุมที่ดีอีกครั้งในราว 12 ปีที่ผ่านมา การทดลองทั้งหลายเหล่านี้แสดงให้เห็นว่าการใช้แผ่นอิเล็กโทรดติดบนศีรษะสามารถทำให้เกิดการเปลี่ยนแปลงทางระบบประสาทอย่างเห็นได้ชัด ซึ่งทั้งนี้ขึ้นอยู่กับทิศทางของกระแสไฟฟ้า*

***วัตถุประสงค์**: เพื่อทบทวนเทคนิคพื้นฐานของเครื่องมือ กลไกการทำงาน และการนำเครื่องกระตุ้นด้วยไฟฟ้ากระแสตรงผ่านกะโหลกศีรษะไปใช้ในการวิจัยทางคลินิก*

***วัสดุและวิธีการ**: รวบรวมการศึกษางานวิจัยเกี่ยวกับการกระตุ้นด้วยไฟฟ้ากระแสตรงผ่านกะโหลกศีรษะจากฐานข้อมูล Medline โดยใช้คำสำคัญคือ "Transcranial direct current stimulation, tDCS, noninvasive brain stimulation, neurophysiologic technique" ตั้งแต่ปี พ.ศ. 2541 ถึง พ.ศ. 2553*

***ผลการศึกษา**: เทคนิคพื้นฐานของเครื่องมือกลไกการทำงาน การนำเครื่องกระตุ้นด้วยไฟฟ้ากระแสตรงผ่านกะโหลกศีรษะไปใช้ในการวิจัยทางคลินิกได้แก่ โรคหลอดเลือดสมอง กลุ่มอาการปวด และความอยาก รวมทั้งอาการข้างเคียง ข้อควรระวังของการกระตุ้นด้วยไฟฟ้ากระแสตรงผ่านกะโหลกศีรษะได้บรรยายไว้ในบทความนี้*

***สรุป**: การศึกษาการกระตุ้นด้วยไฟฟ้ากระแสตรงผ่านกะโหลกศีรษะได้รับความสนใจมากขึ้นเรื่อย ๆ และเป็นที่ยอมรับว่าเป็นเทคนิคที่ไม่ก่อให้เกิดอันตราย ใช้ง่ายและปลอดภัย และจนถึงปัจจุบันผลการใช้การกระตุ้นด้วยไฟฟ้ากระแสตรงผ่านกะโหลกศีรษะในทางคลินิกเป็นไปในทางที่ดีและมีผลข้างเคียงน้อย*