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REVIEW

A description and critical analysis of the therapeutic uses of transcranial direct current stimulation: implications for clinical practice and research

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Abstract: For centuries, since the advent of harnessing magnetic and electrical energies, humans have been applying such energies to various body parts, including the brain, with the goal of improving health. Advancements over the past 2 decades in the production and affordability of such devices that precisely deliver such energies have resulted in novel therapeutic uses. One technique in particular, transcranial direct current stimulation, uses electrodes placed on the scalp to deliver a low electrical current to various areas on the surface of the neocortex. Such electrical currents stimulate neurons, which depending on the area of the neocortex it is applied and certain stimulation parameters, can either excite or inhibit certain functions within the brain that may result in alterations in mood, cognition, and behavior. This article provides an overview of this approach, explains how it is used, describes the hypothesized neurobiomechanisms involved, and explores its therapeutic potential. From this overview, implications for nursing practice and innovative uses for nursing research are posited.

Keywords: tDCS, mood, cognition, electrical stimulation, cognitive training, depression

Introduction

Transcranial direct current stimulation (tDCS) is a noninvasive approach in which a low amperage electrical current is delivered directly to the surface of the neocortex via electrodes attached to the scalp. Mounting evidence suggests that such electrical stimulation of the neocortex produces a neuromodulatory effect within the brain that can either excite or inhibit certain brain functions resulting in alterations in mood, cognition, and behavior. Depending on several factors, including the amplitude of the current, polarity of the amperage (ie, anodal [+/positive] vs cathodal [–/negative]), and placement of the electrodes, these neuromodulatory effects can be achieved.[1] Given these factors including the complexity of brain function, tDCS research represents a challenging but innovative approach to improve and change health care, lifestyle, and wellness. Psychiatric and mental health nurses will undoubtedly be exposed to this emerging technology.

The purpose of this article is to provide a brief description of tDCS. In doing so, first, an overview of applying the actual procedure and the biomechanisms is discussed. Second, a review of its various therapeutic uses in the literature is provided, covering areas such as cognitive improvement, treating mood disorders, and reducing pain. Finally, a critical analysis of these studies is provided along with limitations of their use.

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Overview of tDCS procedure and biomechanisms

Electrical stimulation with tDCS is believed to work by altering such resting membrane potentials across cortical neurons that at a subthreshold level prepare them to depolarize and fire, triggering an action potential. By doing so, tDCS may modulate the firing rate of neurons as well as enhance the strength and quality of neuronal connections in the brain, especially if paired with a learning activity designed to increase (eg, motor function) or decrease (eg, smoking) a particular ability or behavior. By changing the electrical properties of neurons and the release or inhibition of neurotransmitters and neuromodulators, this combination can alter the activity of certain neuronal circuits and neuronal networks (eg, default mode network), which may induce neural plasticity, causing sustained changes in mood, cognition, or behavior.[2–4]

Animal models were first used to explore this relationship between transcortical stimulation and behavioral and physiological outcomes. In the very early work, Creutzfeldt et al[5] demonstrated that application of a positive direct current to the scalp of a cat brain elicited activation of neurons below the surface in the motor and visual cortex but a negative current inhibited activation of neurons. Their research also showed that some of these effects were dose dependent on the amount of current applied. Many years later, Wachter et al[6] experimented with eight Sprague Dawley rats by applying either positive or negative direct currents to these animals' scalps at various amounts/intensities. Using laser Doppler flowmetry to measure cerebral blood flow, these researchers observed the change in cerebral blood flow from baseline to ~30 minutes later after applying such currents. When a positive current was applied to the scalps, cerebral blood flow increased up to ~18% at 50 μA and ~25% at 100 μA. Similarly, when a negative current of 100 μA was applied to the scalps, cerebral blood flow decreased to ~25%. These effects were transient and cerebral blood flow returned to baseline levels in time; however, these data demonstrate the ability of tDCS to produce actual physiological changes.

Although there are many variations of the tDCS protocol (aka, montage), the basic components are represented in Figure 1. The tDCS device is typically powered by a battery, thus preventing the risk of shock or electrocution. One

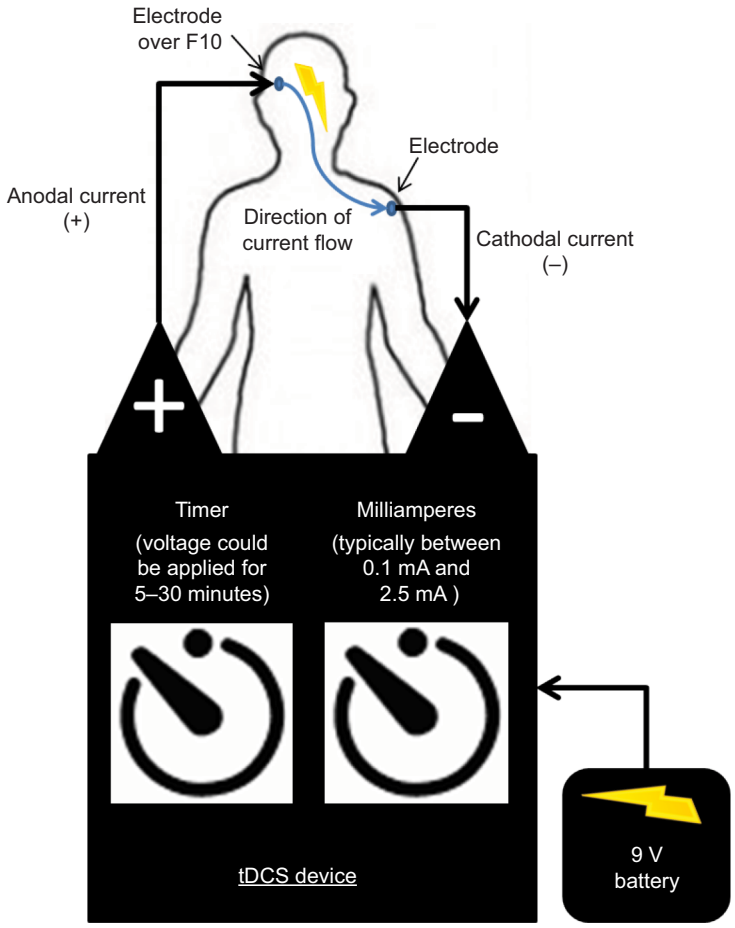

Figure 1 Basic overview of the tDCS protocol with an example of F10/contralateral upper arm montage.
Abbreviation: tDCS, transcranial direct current stimulation.

electrode is placed on the target brain area, and the second return electrode is placed on the area where the electrical current will leave the body, typically another part of the brain or a neutral place such as a shoulder.[7] The electrodes are embedded in saline-soaked sponges and fastened via elastic straps that hold them in place during the session. The use of either the saline solution or gels is to prevent contact burn with the electrodes and assist with conductance of the electrical current. A predetermined amount of electricity is provided and often paired with a learning or therapeutic activity that is designed to augment a particular skill or behavior.[7]

For example, in a typical study, Clark et al[7] used a series of single-blind, randomized studies to examine the effects of tDCS on learning a complex visual task (ie, identifying concealed objects) in 96 healthy adults. Participants were trained to identify where lethal objects such as bombs were hidden in the pictures presented to them based on the feedback by playing a virtual reality environment game called "DARWARS Ambush!" These researchers fastened an anodal electrode over the right inferior frontal cortex near F10 (ie, directly over the sphenoid bone inferior to F8; Figure 1). This region of the brain is associated with executive functioning and attention. The current exited the body through the placement of the cathodal electrode on the contralateral upper left arm. Participants received the current 5 minutes before the training session (this is considered priming the brain for learning) and continued to receive the stimulation 30 minutes into the training scenario. These researchers found that those participants assigned to the 2.0 mA condition exhibited significantly better learning (ie, detecting more concealed objects) than those assigned to the 0.1 mA (sham) condition.

Other considerations of tDCS, already alluded to, include: 1) application of either anodal or cathodal current, 2) placement of electrodes, and 3) amount of electricity. First, the application of either anodal or cathodal current to the target area must be considered. The direction of the flow of the electrical current associated with tDCS determines whether it increases or decreases brain excitability. Stimulation of brain areas is dependent on how the current travels from positive/anodal (+) to negative/cathodal (–). Generally, anodal application to a targeted brain area produces excitability-enhancing effects; likewise, cathodal application to a targeted brain area produces inhibitory-enhancing effects.[3,8]

Second, the placement of electrodes is made through precise measurements using the International 10–20 system of electrode placement (Figure 2). It is important to note that the placement of the electrodes on targeted brain areas can have both excitatory and inhibitory effects, depending on the neuronal function. In fact, some brain areas when

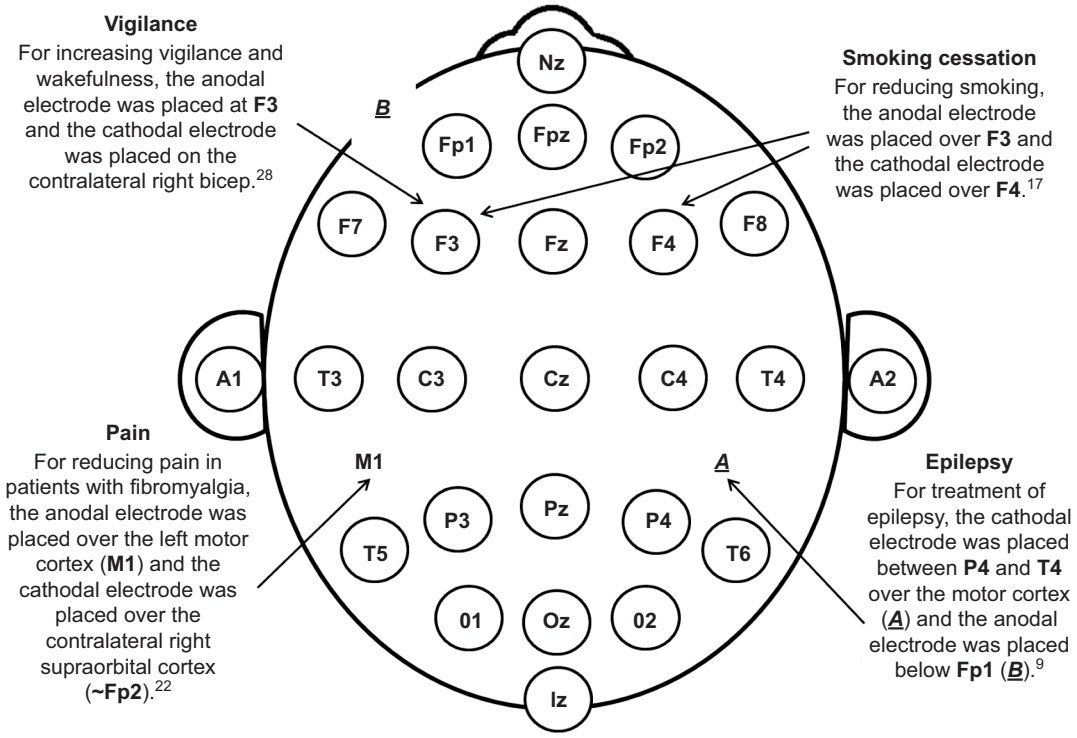

Figure 2 International 10–20 system of electrode placement and examples of anodal and cathodal electrode placements.
Abbreviations: Nz, Nasion; Iz, Inion.

stimulated activate the regulation and inhibition of other brain areas, so in essence, the excitability-enhancing effects of anodal stimulation can create an inhibition in some mood, cognitive, or behavior outcomes; likewise, the opposite can be observed with the inhibitory-enhancing effects of cathodal stimulation. It is important to note that even in certain brain structures, there are inhibitory and excitatory neuronal pathways that are needed to regulate particular functions or maintain homeostasis; for that reason, tDCS is sometimes used to inhibit neuronal activity as well. For example, in one case study of an 11-year-old girl with epilepsy, cathodal tDCS at 2.0 mA was applied to the right motor cortex (between P4 and T4) for 20 minutes a day for 10 days over a 2-week period (Figure 2). By using the inhibitory properties of tDCS, this patient experienced a clinically meaningful reduction in seizures from eight per month to one per month.[9] Thus, it depends upon the interaction of the electrode placement and the particular function of the brain area being stimulated.

Third, the amount of current applied is also an important component, both in terms of amperage and exposure time.[10,11] In a systematic review of tDCS, Elmasry et al[10] reported that researchers trying to improve cognition in their participants varied from as little as one session of 17 minutes of tDCS exposure at 1.0 mA to as much as 18 sessions of 30 minutes of tDCS exposure at 2.0 mA. In the study by Clark et al[7] mentioned earlier, they provided 30 minutes of tDCS with a cognitive training at various amperages (ie, 0.1 mA, 0.6 mA, and 2.0 mA); they concluded that 2 mA produced the greatest therapeutic cognitive gains. A review of the literature shows that many researchers prefer the 2.0 mA level as the optimal therapeutic dose while balancing safety and patient burden;[7,10,11] yet the timing of application, duration, and dosage of sessions required to achieve an optimal therapeutic effect remain a question for further research.

Therapeutic uses

tDCS may embody several therapeutic uses and advantages in being used as a therapy or adjuvant therapy to treat various conditions. Although not exhaustive, the following areas are highlighted to simply demonstrate the potential therapeutic utility of tDCS: depression and mood disorders, smoking cessation, pain, cognition, and Parkinson's disease.

Depression/mood disorders and tDCS

Major depressive disorder is characterized by alterations in various cortical and subcortical areas, particularly the prefrontal cortex. By stimulating this area, researchers have shown that tDCS can reverse or mitigate such pathological alterations back to normal in the general psychiatric population.[12] For example, in a sample of 120 antidepressant-free participants with moderate-to-severe depression, Brunoni et al[13] examined the combined effect of tDCS and an antidepressant (sertraline) on depressive symptoms. These researchers randomized participants into four groups: 1) sham tDCS, 2) active tDCS + placebo, 3) sham tDCS + sertraline, and 4) active tDCS + sertraline. From baseline to 6 weeks later, using the Montgomery–Asberg depression rating scale, compared to the placebo group, those in the tDCS + sertraline group improved on average by 11.6 points, those in the tDCS-only group improved by 5.6 points, and those in the sertraline-only group improved by 2.9 points. This study shows that tDCS may accentuate the effects of antidepressants, providing further evidence of the most optimal tDCS effects being observed when this approach is an adjunct with other therapies.

The use of tDCS may be particularly advantageous to certain clinical populations, based on their unique characteristics and medical profile, such as those with HIV. In a pilot study of eight adults with HIV suffering from major depressive disorder, Knotkova et al[14] administered tDCS for ten sessions over a 2-week period. These researchers observed that depression scores were significantly reduced after this brief period of time; unfortunately, this study lacked a control group. Nonetheless, this study is relevant because the prevalence of depression and anxiety in this population is ~40% and 20%, respectively, which is associated with poor medication adherence and reduced quality of life.[15] Fortunately, tDCS may have a faster therapeutic onset than most antidepressants that take weeks to reach a therapeutic level. Furthermore, tDCS may be the therapy of choice for depression, particularly for those who cannot tolerate the side effects (eg, sexual dysfunction) of antidepressants. In addition, in the HIV population, comorbidities including renal and hepatic diseases, and high medication burden are common; therefore, avoiding additional medications to treat depression is preferred in lieu of possible medication interactions, polypharmacy, and additional pharmacological liver and kidney burden. In fact, tDCS does not appear to have any medication interactions, although some medications such as rivastigmine (an acetylcholine reuptake inhibitor used to treat Alzheimer's disease) may abate the efficacy of tDCS.[13,16]

Smoking cessation and tDCS

One example of tDCS changing behaviors and improving wellness is observed in smoking cessation and aberrant, unhealthy cravings. Boggio et al[17] randomized 27 smokers to receive either the active or sham tDCS condition while they

were shown cues to provoke smoking cravings. The 2.0 mA anodal current was placed over the left dorsolateral prefrontal cortex (F3) and exited via the cathodal electrode placed at F4 (Figure 2). This placement of tDCS was administered in 20-minute sessions over five consecutive days. The dorsolateral prefrontal cortex is intricately involved with the processing of cravings associated with substances such as alcohol, cocaine, and opiates (ie, dopamine-driven alterations). Hypothetically, stimulating this area of the brain can also induce reward-related activation, which can reduce such cravings. Participants in the active condition experienced a small, but significant, reduction in the amount of cigarettes smoked compared to those in the sham condition. Furthermore, those in the active condition also reported a greater decrease in such cravings. A recent study using such electrical stimulation in a mouse model also demonstrated beneficial effects on chronic nicotine consumption.[18] These studies on tDCS and smoking cessation suggest that tDCS may be efficacious in other addictions, such as other drugs and overeating.[19–21]

Pain and tDCS

Pain reduction is also a targeted therapeutic outcome of tDCS. In a typical study, Foerster et al[22] administered tDCS to 12 patients with fibromyalgia. The dosage consisted of 2.0 mA with the anodal electrode placed over the left motor cortex (M1) and the cathodal electrode placed over the contralateral right supraorbital cortex (~Fp2; Figure 2). Compared to the sham condition, when patients received the active tDCS treatment, a significant decrease was observed in clinical pain scores. Using proton magnetic resonance spectroscopy, compared to sham tDCS treatment, Foerster et al observed lower levels of glutamate + glutamine in the anterior cingulate and the thalami as well as increased levels of Gamma-Aminobutyric Acid in the anterior insula as a result of the treatment. In fact, changes in the levels of glutamate + glutamine in the anterior cingulate significantly correlated with changes in the clinical pain scores. These researchers concluded that levels of glutamate/glutamine, *N*-acetylaspartate, and GABA may be modified by tDCS in that these brain metabolites may play a critical role in pain regulation in such patients with fibromyalgia.

Besides fibromyalgia, tDCS-induced pain relief has been observed with other conditions including traumatic spinal cord injuries,[23] complex regional pain syndrome type 1,[24] neuropathy relating to multiple sclerosis,[25] and chronic migraines.[26] In a systematic meta-analysis of 18 studies that used either tDCS or a related transcranial device (ie, transcranial magnetic stimulation), Zaghi et al[27] found an average effect size of –0.86 across studies. This meta-analysis emphasizes that such transcranial devices have a moderate effect in providing pain relief.

Cognition and tDCS

Capitalizing on both the success of cognitive remediation therapy (ie, computerized cognitive training) and tDCS, researchers have combined these two approaches to maximize the cognitive training effects of these therapies. A systematic review of 13 studies using a combination of tDCS + cognitive training has shown synergistic effects of enhancing cognitive gain beyond cognitive training alone. Furthermore, some studies have even demonstrated increased transfer effects beyond that which was trained and that such training effects were durable over time.[10]

One reason why tDCS may have been shown to improve cognition is because it may increase vigilance and attention; this can be especially observed in those who experience extended wakefulness. In a sample of 30 active-duty military participants, McIntire et al[28] recruited them to stay awake for 30 hours and randomized them into one of three groups: 1) sham tDCS + caffeine gum, 2) active tDCS + placebo gum, and 3) sham tDCS + placebo gum (the true control group). The tDCS dosage consisted of 30 minutes of 2 mA with the anodal electrode placed at F3 and the cathodal electrode placed on the contralateral right bicep (Figure 2). These researchers observed that on measures of psychomotor reaction time and short-term memory, the active tDCS and caffeine gum groups performed similarly and better than those randomized to the sham tDCS/placebo gum group. This study demonstrates that tDCS as well as caffeine may work in promoting wakefulness and cognitive vigilance.

Parkinson's disease

Parkinson's disease produces both cognitive and motor symptoms which may be somewhat amenable to tDCS. In a small study of 18 adults with Parkinson's disease, Doruk et al[29] found that placement of anodal current over either the left or right dorsolateral prefrontal cortex, compared to a sham control group, improved executive functioning over a 1-month period. Although such cognitive improvements have often been shown to result from tDCS, improvements in motor symptoms may be more limited.

In a recent *Cochrane Database Systematic Review*, Elsner et al[30] examined the effects of tDCS on motor and nonmotor symptoms of idiopathic Parkinson's disease; only six randomized controlled studies met the entry criteria and were examined. Although there was limited evidence of tDCS being effective in improving both motor and nonmotor symptoms,

these researchers concluded that there is insufficient evidence at this time to apply tDCS for the treatment of Parkinson's disease. Albeit, a recent study by Kaski et al[31] founded that tDCS combined with physical training may improve gait velocity compared to physical training alone; yet, this study was very underpowered and ungeneralizable with a small sample of only 16 participants. Yet, other researchers continue to examine combinations of physical training (ie, progressive resistance training) with tDCS for the treatment of Parkinson's disease-related motor symptoms.[32]

Critical analysis

Despite the optimistic findings presented thus far, the clinical use and adoption of these devices must be critically considered in several regards, including the research methodology, safety concerns, and the complexity of emerging spin-off tDCS variations.

Research methodology

Several meta-analyses evaluating the efficacy of tDCS on general neurological effect (*N*=94 studies; Nitsche et al[11]), motor and cognitive function (*N*=46; Flöel[33]), pain (*N*=18 studies; Zaghi et al[27]), and combination of tDCS + cognitive training (*N*=13; Elmasry et al[10]) have shown overall validation for changing brain chemistry and improving targeted outcomes. In fact, some of these studies show that such improvements remain 6 months after being treated with tDCS.[34] Yet, limitations in many of these studies include: 1) small sample sizes including single-patient designs, 2) lack of a control group, and 3) limited time frame for sufficient longitudinal analysis. In addition, with various dosage parameters across studies, it remains a challenge to compare between studies; in that regard, there is no clear dosage parameter established. A few studies also find no effect when using tDCS.[35,36] In addition, of particular interest is that sex differences have been observed with tDCS.[37] Finally, some medications were observed to suppress (eg, carbamazepine and dextromethorphan) or enhance (eg, pergolide and amphetamine) the effects of tDCS,[2,3,38–40] which adds to the complexity of their use in clinical settings. These research methodology concerns must be considered when interpreting the tDCS literature.

Safety concerns

Obviously, there are safety concerns of exposing the scalp to even a small amount of electrical current. Although there are some case reports of burns or skin lesions as a result of tDCS,[41] these seem to be isolated incidents and may be related to the amount of milliamps or particular patient characteristics. In fact, tDCS delivers an extremely low electrical current to the scalp (this is the equivalent of 1/100 of that needed to power a lightbulb), with the effects being quite subtle on their own.[42] But in general, tDCS appears to be safe, well tolerated, and easy to administer.[43,44] As reported by Poreisz et al[1] who applied tDCS to the parietal, motor, and occipital cortex in 567 participants and patients (ie, healthy participants [75.5%], tinnitus patients [9.8%], migraine patients [8.8%], and poststroke patients [5.9%]), no participant or patient terminated/refused the use of the tDCS. During the administration of tDCS, mild tingling was the most common complaint (70%), followed by moderate fatigue (35%), and mild itching under the electrode (30%). After the administration of tDCS, headache was the most common complaint (12%), followed by nausea (3%) and insomnia (1%).

To minimize some of the safety concerns, clinicians and researchers can assess the level of discomfort during the administration of tDCS. For example, in the study by Clark et al[7] reported earlier, during the treatment protocol, participants were asked to describe the physical sensation of the tDCS after 5 minutes and 15 minutes into the session using the following descriptors: "0) no sensation, 1) cold, 2) some tingling, 3) warm, 4) lots of tingling/some itching, 5) very warm, 6) lots of itching, 7) burning (like a sunburn), 8) burning (like scalding water), 9) 'hurts a lot'". An indication of 7 or higher resulted in immediate termination of the study. In addition, this and other studies typically exclude those with metal implants or implanted electrical devices such as pacemakers because of "possible" effects of such devices, although it is not clear whether tDCS or other electrical stimulation devices would pose a risk when administered to those with such implants or devices.[43,45,46] Likewise, studies sometimes exclude those who have epilepsy for concerns of inducing a seizure; however, tDCS has been shown to exert antiseizure effects if used correctly.[9,47] In addition, since it is not clear how tDCS may affect the developing brain, its use with children should be used with caution.[48]

In addition to these obvious safety concerns, unfortunately some people are either building their own tDCS devices or buying inexpensive tDCS devices online to augment cognitive abilities or "treat themselves" for pain or other maladies.[49] Yet, caution must be applied in using such devices, especially in the hands of novices who may actually induce unanticipated consequences such as inducing depression or attentional deficits. For instance, Cohen Kadosh et al[50] reported that tDCS improved certain mathematical abilities in a group of participants; unfortunately, those who

experienced such improvements actually experienced a decline in other mathematical skills as a result. Needless to say, the brain is a complex organ and altering the function in one area may cause an unforeseen change in another. This application of tDCS is further complicated by the interaction of drugs whether they are illicit or illegal, age, smoking status, shape of the head, and other factors that could potentially influence the effects of tDCS.[49] However, in general, tDCS does not seem to possess any detrimental pharmacological interactions.[1,43] Still, as tDCS is slowly incorporated into clinical practice, caution should be heeded as evidence-based guidelines and policies are generated for tDCS. Much more research is needed on clinical applications of and appropriate settings for tDCS as well as ethical considerations for what situations and conditions such treatment should be used. For example, if tDCS becomes approved for clinical treatment of various disorders, should it be used in those without such conditions to improve and maximize certain brain functions?

Other transcranial stimulation treatments

Besides such safety concerns, the field of transcranial stimulation treatments continues to grow. Although the focus of this article is on the basic tDCS montage where the primary mechanism of affecting neuronal functioning is through current polarity, it is important to acknowledge other transcortical devices such as transcranial alternating current stimulation (tACS) and transcranial random noise stimulation (tRNS) that are being developed with encouraging results. In these other approaches, the main cause of action is not through current flow but through oscillatory current intensity and current frequency. In tACS, specifically, an alternating (+, −, +, −, etc) low current intensity (<1 mA) is delivered for a specific duration.[10] tACS may work by altering the rhythmic oscillations that normally occur in the brain implicated in cognitive functioning. In tRNS, specifically, a frequency spectrum between 0.1 Hz and 640 Hz is delivered over a normally distributed random level. As with tDCS, it is believed that tRNS increases cortical excitability, possibly due to long-term potentiation-like mechanisms. For example, to examine neural plasticity using a perceptual learning task as a proxy, Fertonani et al[51] compared various settings of tDCS and tRNS to determine which one is better at inducing neural plasticity. They randomized 107 healthy adults to one of six groups: 1) anodal tDCS, 2) cathodal tDCS, 3) high-frequency tRNS (100–640 Hz), 4) low-frequency tRNS (0.1–100 Hz), 5) high-frequency tRNS placed over Cz and assumed not to be involved with the perceptual learning task, and 6) sham condition. The dosage for all of these (except sham) was set at 1.5 mA and placed on the occipital cortex (~3 cm above the inion around Oz; Figure 2) except for the group where it was placed over Cz. Otherwise, presentation of the perceptual learning task and the placement of the nontarget/reference electrode on the right arm were held constant between groups. In general, it was observed that cognitive performance improved the most with the high-frequency tRNS, then low-frequency tRNS, followed by anodal tDCS; the other conditions (cathodal tDCS, high-frequency tRNS over Cz, and sham tDCS) experienced the least improvement. This and other studies suggest that the use of high-frequency tRNS may be the same or even more efficacious than standard tDCS protocols;[52] albeit, more studies are needed to compare the therapeutic value between these related approaches. Furthermore, as a concern for clinical practice and research, questions remain for all of these transcranial devices in terms of dosage. How many sessions are needed? What is the amount of current, timing of current, and/or hertz needed to result in optimal therapeutic change?

To further complicate such dosage questions, it should be mentioned that tDCS is but one of many electrical devices that may be used to change behavioral and neuronal functioning. Such devices include transcranial magnetic resonance stimulation, repetitive transcranial magnetic resonance stimulation, transcutaneous nerve electrical stimulation, galvanic vestibular stimulation, transcranial micropolarization, and others (for more information, refer to reviews from Guleyupoglu et al[53] and Novakovic et al[54]).

Conclusion

Clearly, tDCS and other variations of electrical therapeutic stimulation represent a novel and still relatively new area of improving health and well-being for many patient populations. Application of electrical therapeutic stimulation in conjunction with other treatments may provide unique and synergistic effects on patient health outcomes as well. Yet, the application of the device on certain brain areas requires skill and an understanding of basic neurology for it to be effective; novices using the device on their own brains should be cautioned that application may actually cause an unexpected and undesirable effect. As these devices become more available and commonly used in clinical practice, education and policies will need to be developed to help regulate their proper and safe use in patients.

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Disclosure

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