The Effect of Transcranial Direct Current Stimulation (tDCS) on Seizure Control and Epilepsy Prevention

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SUMMARY

Introduction. Epilepsy is one of the most common neurological diseases. It is an uncontrollable neuronal activity of different parts of the brain leading to convulsion and/or fainting. Although epileptic seizure control and therapeutics have significant advances, 20% - 30% of individuals still have uncontrolled seizures. Patients under the medication's control are not free from the drug's side effects and complications. Epileptic patients experience many different challenges. Transcranial direct current stimulation (tDCS) is a safe and non-invasive brain stimulation method applied in drug-resistant seizures and epilepsies. It transmits positive/negative electrical current toward deep brain parts, modulating their electrical activity. Methods. This is a review article. All relevant articles which were accessible were reviewed. The effectiveness of tDCS in preventing epilepsy in patients undergoing seizures was reviewed in this article. Conclusion. According to the studies, this method can probably be an auxiliary method in preventing and treating seizures. As epileptic seizures were induced and confirmed in some studies after the application of tDCS, the method should be cautiously applied.

Keywords: seizure, convulsion, prevention, epilepsy, tDCS

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INTRODUCTION

Seizure

Seizure is a common neurological condition caused by the abnormal, excessive, and hypersynchronous electrical activity of neurons in the brain (1, 2). Convulsive symptoms that occur during a seizure depend on the location of the abnormal electrical activity (3). Seizures are classified as generalized seizures, focal seizures, or epileptic spasms. Generalized seizures are generated within bilaterally distributed brain networks, whereas focal seizures originate within networks restricted to one cerebral hemisphere. The origin of epileptic spasms is unknown (2). In the new classification of the International League Against Epilepsy, features such as the level of awareness during seizure and the level of body movement, in addition to the origin of the seizure in the brain, have been used to classify seizures (3). From an etiological standpoint, seizures can be provoked or unprovoked. Provoked seizures can be caused by an acute symptomatic condition such as a brain insult, systemic metabolic or toxic, while unprovoked seizures are those that occur in the absence of provocative factors or are caused by a static or progressing injury (4).

Pathophysiology

A seizure occurs when neurons fire simultaneously in a part of the brain or throughout the brain when networks are disorganized or disrupted by structural changes, metabolic disturbance, or infection (5). An imbalance between inhibitory and excitatory neurotransmission is one of the main factors in the development of epileptic seizures (6). Glutamate, the main excitatory neurotransmitter, induces overexcitation via the NMDA receptors, whereas GABA, the major inhibitory neurotransmitter, inhibits overexcitation by activating GABAA receptors. Seizures may occur due to increased excitation or decreased inhibition in the brain (7).

The most important causes of seizures in children are genetics, anomalies of cortical development, and injury following perinatal insult (5). In adults without genetic susceptibility to epilepsy, the common causes of seizures are brain tumors, traumatic brain injury (TBI), and encephalitis/meningitis (8). In old patients, epilepsy is generally caused by brain tumors, head trauma, and primary neurodegenerative diseases (9).

Epilepsy

Epilepsy is one of the most common brain diseases, with many causes (10). Recurrent, unprovoked seizures are a hallmark of epilepsy (2). Epilepsy may result from several factors, such as stroke, tumors, infections, or traumatic brain injury with post-traumatic epilepsy (11). Comorbidities such as autism and intellectual disability are more common in patients with epilepsy (up to 20 times) than in the general population (12). Severe and recurrent seizures, such as status epilepticus, disrupt the blood-brain barrier and promote neuroinflammation, which in turn contributes to epileptogenesis (13). Damage or death of neurons and changes in neural networks might result from status epilepticus (SE), depending on the type and duration of the seizure (14). The cause of epilepsy, in almost 50% of cases, is unknown (5).

In 2017, the ILAE classified epilepsies into four main types, including focal, generalized, combined generalized and focal, and an unknown group (15). According to the practical clinical definition of epilepsy by the ILAE, “epilepsy is considered to be a disease of the brain defined by any of the following conditions: (1) at least two unprovoked (or reflex) seizures occurring > 24 h apart; (2) one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next ten years; (3) diagnosis of an “epilepsy syndrome” (16). The term “epilepsy syndrome” refers to a collection of clinical characteristics that usually occur together. This includes seizure type(s) along with the age of onset, electroencephalogram (EEG) findings, brain imaging features, genetic factors, triggering factors, and response to antiepileptic drugs (2, 15).

A critical issue that requires immediate attention is that the majority of people with epilepsy live in low-income countries with inadequate epilepsy management. There is a lack of adequate medical facilities and trained medical personnel in these countries (17). People with epilepsy are at risk of a variety of mental disorders, so treating epilepsy is very important (18). Treating epilepsy includes surgery, medication, a ketogenic diet, and neuromodulation. More than 30% of epilepsy patients are re-
sistant to medication (19). Symptomatic treatments include: A) anti-seizure treatment: a treatment that prevents or decreases seizure frequency and severity, regardless of the underlying epileptic state or progression of the disease; B) anti-comorbidity treatment: a medication that relieves or reverses symptoms associated with epilepsy comorbidities such as cardiovascular events, neuropsychiatric problems, and neurocognitive impairment (20).

Epilepsy etiology

The International League against Epilepsy has defined six etiological categories: 1. Structural; 2. Infectious; 3. Genetic; 4. Metabolic; 5. Immune; and 6. Unknown. These are not hierarchical, and more than one factor can be involved (21).

Pharmacological treatment of epilepsy

Antiepileptic medications are the mainstay of epilepsy treatment; medical therapy may last for years or even a lifetime (22). Acetazolamide, carbamazepine, clonazepam, clorazepate, and lamotrigine are the examples of antiepileptic medications approved in the United States and Europe. Other medicines, such as lorazepam or diazepam, may be prescribed in some situations (23).

Mortality

Epilepsy patients are at a higher risk of premature death. The life expectancy of patients with symptomatic epilepsy may be reduced by up to 18 years. Trauma, suicide, sudden death, and pneumonia are more common in epilepsy patients than in healthy subjects. Evidence shows that the mortality rate is higher in resource-poor countries than in developed countries (17).

Epidemiology

The probability of experiencing an epileptic seizure during one’s lifetime is approximately 10% (24). While the vast majority of the people who have a seizure do not have epilepsy, the prevalence of epilepsy disease is around seven patients per 1000 people, with a higher rate in low-income countries (14). The lifetime prevalence rate of epilepsy is reported to be between 0.7 and 1.0%, with a high incidence in children and older people (25).

The incidence of epilepsy in developed countries is higher in infants and older people (26). There is a significant difference in the prevalence and incidence of epilepsy in high and low-income countries, and low-income countries are more affected (5). Inadequate health services, improper sanitation, and brain infections could contribute to an increased incidence of epilepsy in low-income countries (27). Risk factors vary by geography and age; endemic parasitic diseases such as neurocysticercosis and falciparum malaria are preventable epilepsy risks all over the world (17).

Epilepsy may potentially increase the risk of stroke (28). Genetic differences, increased trauma rates, higher rates of parasitic infections, and the lack of effective treatment also contribute to epilepsy (29). The lack of anti-seizure drugs is another factor contributing to the prevalence of epilepsy in a number of countries (30). Epilepsy has different effects at different ages, although it is most prevalent in two age groups: 5 to 9 years old and about 80 years old (31, 32).

Epileptic brain waves variations

The electroencephalogram can reveal epilepsy by displaying changes in brain electrical activity. Each variation in brain waves can determine a specific type of epilepsy (33). Anterior temporal spikes are ascribed to mesial temporal lobe epilepsy, generalized 3-Hz spike-wave complexes to absence epilepsy, generalized polyspikes with more than 4-Hz spike-wave complexes to juvenile myoclonic epilepsy, generalized slow spike-wave complexes to Lennox-Gastaut syndrome, extratemporal regional polyspikes to focal cortical dysplasia, and hypsarhythmia to West syndrome (34).

The tDCS apparatus

Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation method that delivers a weak electrical current to the scalp (35, 36). The current intensity of tDCS is so low that a person may not even feel the current passing through the scalp (37). The current intensity is usually between 1 and 2 mA (38). The tDCS has different types including anodal tDCS (a-tDCS), cathodic tDCS (c-tDCS), and sham tDCS (39).

Transcranial electrical stimulation’s ability to modulate brain function has attracted considerable
scientific attention (40). The tDCS modulates cortical excitability in a polarity-dependent manner by transmitting weak direct currents through the scalp using two electrodes placed on the head. For the primary motor cortex, as well as other areas, the a-tDCS, which refers to the inward current in the target area, leads to increased cortical excitability. In contrast, the c-tDCS, which refers to the outward current in the target area, reduces it (41). Historically, Plato and Aristotle, two ancient Greek philosophers, were both aware of torpedo fish’s electrical discharge capacity to induce therapeutic effects. Utilizing live torpedo fish on the scalp to alleviate headaches might be considered an early form of tDCS. For more than ten centuries, the electrical stimulation of fish has been used to treat epilepsy, diarrhea, headaches, and even gout (40).

SEARCH STRATEGY

Authors used PubMed, ScienceDirect, Scopus, and Google scholar search engines to reach all published papers pertaining to the subject. Keywords were: seizure, convulsion, transcranial direct current stimulation, anti-epileptogenesis, epilepsy prevention, and related words and abbreviations. Articles that focused just on the tDCS influence on epilepsy treatment and not prevention were excluded. Totally, 18 related articles were found, and the authors presented and analyzed them with no bias.

THE TDCS AND SEIZURE

Animal studies

A series of studies were performed on rats to investigate the effect of tDCS on seizures. In a study, status epilepticus was induced in rats by kainic acid, and rats were exposed to cathodic tDCS or stimulation for five days to investigate the effects of c-tDCS on interictal spike changes, EEG oscillations, and post-epileptic outcomes. The c-tDCS electrode pin was plugged into a plastic cannula placed on the central sagittal fissure above the dorsal hippocampus. Results showed that recurrent c-tDCS reduced interictal spikes, increased low-frequency delta oscillation, decreased high-frequency gamma and beta oscillation, and lowered hippocampal brain-derived neurotrophic factor (BDNF) protein expression. These results suggest that c-tDCS have an inhibitory effect on neuronal excitability in the epileptic brain by enhancing the endogenous delta oscillation (42). In 2020, researchers examined the effect of tDCS on seizure severity, EEG activity, and post-SE outcomes in rats' kainic acid-induced SE model. The c-tDCS was applied over the dorsal hippocampus. This study detected two EEG patterns in the hippocampal CA1 region of SE rats: high-frequency polyspikes in a range of gamma frequencies and low-frequency spike-and-wave complexes. Seizure severity, high-frequency oscillation, chronic spontaneous spike activity, mossy fiber sprouting, and hippocampal BDNF protein expression decreased after tDCS treatment in SE rats (43). It seems that a decline in hippocampal BDNF prevents epileptogenesis (44-46), and in this way, tDCS prevents seizure conversion to epilepsy.

Another study examined the effect of c-tDCS in rats using a pentylenetetrazol (PTZ)-induced SE model. This study aimed to determine whether c-tDCS prevents seizures, increases cortical GABAergic inhibition, and promotes the efficacy of lorazepam. After the initial PTZ administration and subsequent c-tDCS, the rats received a second PTZ injection. Results showed that 1 mA c-tDCS reduced epileptic spike waves in EEG, and following the second PTZ challenge, it prevented clinical seizure occurrence. Compared to tDCS or lorazepam alone, combining c-tDCS and a subtherapeutic dose of lorazepam after PTZ injection resulted in effective seizure suppression and improved clinical outcomes. Additionally, c-tDCS prevented the loss of the inhibitory GABAergic system in the motor cortex caused by PTZ injection, as measured by paired-pulse transcranial magnetic stimulation (ppTMS) (47). The GABAergic system reinforcement restrains epileptogenesis (48), especially in adults (49). Therefore, epileptic motor complications may be alleviated.

Kamida et al. investigated the effects of c-tDCS on the frequency of convulsions, neuronal loss, mossy fiber sprouting, and spatial memory function in immature rats after pilocarpine-induced status epilepticus. The results of this study showed that over a period of two weeks, c-tDCS significantly decreased the frequency of convulsions in SE rats. The behavioral examination also showed that c-tDCS positively affected SE rats’ improved Morris water maze performance. Additionally, histological examination revealed hippocampal cell loss, and supra-granular and CA3 sprouting were reduced after c-
tDCS (50). Also, the effects of tDCS on seizure severity and cognitive were evaluated by the same researcher and colleagues in fully amygdala-kindled rats. One day following the last c-tDCS treatment, it significantly reduced the seizure stage and the after-discharge threshold and cognitive performance. According to the findings, c-tDCS has anticonvulsant and positive cognitive effects for at least one day after treatment in amygdala-kindled rats (36).

Another study investigated the effect of tDCS on the cerebral cortex of rats with pentylenetetrazol-induced seizures. In kindling rats, c-tDCS prevented the onset of generalized clonic-tonic seizures and the development of generalized seizures. Additionally, there was a decrease in the

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<th>Author/year</th>
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<tr>
<td>Wu et al. 2021</td>
<td>Sprague-Dawley male rats</td>
<td>Status epilepticus induced by kainic acid</td>
<td>c-tDCS above the dorsal hippocampus and a-tDCS at the dorsal shoulder</td>
<td>c-tDCS: 1 mA, 30 min per day and sham tDCS: 1 mA, 30 s per day for 5 consecutive days</td>
<td>c-tDCS reduced interictal spikes, increased low frequency delta oscillation, decreased high frequency gamma and beta oscillation, decreased hippocampal brain-derived neurotrophic factor (BDNF) protein expression</td>
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<tr>
<td>Dhamne et al. 2015</td>
<td>Long Evans male rats</td>
<td>Status epilepticus induced by pentylenetetrazol</td>
<td>Active electrode (disc electrode) on the dorsal scalp, and reference electrode (sponge electrode) under the ventral torso</td>
<td>Sham, cathodal 1 mA, or cathodal 0.1 mA; for 20 min</td>
<td>c-tDCS reduced epileptic spike waves in EEG, prevented clinical seizure occurrence after second PTZ challenge, and prevented motor cortex GABAergic loss. c-tDCS+ subtherapeutic dose of lorazepam was more effective in seizure suppression and improved clinical outcomes.</td>
</tr>
<tr>
<td>Kamida et al. 2013</td>
<td>Wistar male rats</td>
<td>Amygdala-kindling model of temporal lobe epilepsy with electrical stimulation</td>
<td>Epicranial electrode at 1.5 mm right and 2 mm anterior to the bregma</td>
<td>c-tDCS: 200 μA, 30-min daily session for 1 week</td>
<td>c-tDCS reduced seizure stage, reduced after-discharge duration, enhanced after-discharge threshold and improved cognitive performance</td>
</tr>
<tr>
<td>Wu et al. 2020</td>
<td>Sprague-Dawley male rats</td>
<td>Status epilepticus induced by kainic acid</td>
<td>c-tDCS over the dorsal hippocampus and a-tDCS at the dorsal shoulder</td>
<td>c-tDCS: 1 mA, 30 min per day, and sham tDCS: 1 mA, 30 s per day for 5 consecutive days</td>
<td>c-tDCS decreased seizure severity, high-frequency oscillation, chronic spontaneous spike activity, mossy fiber sprouting, and hippocampal BDNF protein expression</td>
</tr>
<tr>
<td>Godlevsky et al. 2017</td>
<td>Wistar male rats</td>
<td>Pentylenetetrazol-induced kindling</td>
<td>c-tDCS on the skull surface oriented to the cerebellar cortex and a-tDCS: on the abdominal skin</td>
<td>Direct current of 600 μA for 15 min</td>
<td>c-tDCS prevented clonic-tonic and generalized seizures. Also, c-tDCS reduced ictal discharge duration and increased seizure latency in brain structures.</td>
</tr>
<tr>
<td>Regner et al. 2020</td>
<td>Wistar male rats</td>
<td>Pentylenetetrazole-induced kindling</td>
<td>Cathodal electrode on parietal cortex and anodal electrode at supraorbital area</td>
<td>a-tDCS or c-tDCS: 0.5 mA, 20-min daily session for 10 days</td>
<td>c-tDCS + low-dose diazepam increased the latency to the first clonic forelimb seizure. c-tDCS alone or + low-dose diazepam increased cortical TNF-α, IL-1β, NGF, and BDNF and decreased hippocampal IL-1β and mortality rate.</td>
</tr>
<tr>
<td>Kamida et al. 2011</td>
<td>Wistar male rats</td>
<td>Status epilepticus induced by lithium-pilocarpine</td>
<td>Active electrode: 1.5 mm to the right and 2 mm anterior to the bregma and reference electrode: at the back of the neck</td>
<td>c-tDCS: 200 μA, 30-min daily session for 2 weeks</td>
<td>c-tDCS reduced the frequency of convulsions, loss of hippocampal cells, CA3 and supragranular, sprouting, and improved performance in the Morris water maze.</td>
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Table 1. Overviewing the tDCS effects on seizure control in animal subjects
duration of ictal discharges and an increase in the latency of seizures in brain structures after c-tDCS treatment (51).

An animal investigation examined the effect of a-tDCS and c-tDCS on behavioral and neurochemical parameters in PTZ-induced kindling rats. Additionally, the effect of a-tDCS and c-tDCS was evaluated in conjunction with or without diazepam to ascertain a possible synergism between them. Either a- or c-tDCS did not reduce the occurrence of clonic seizures in the forelimb. However, the first clonic forelimb seizure latency increased when c-tDCS was combined with low-dose diazepam. Also, c-tDCS alone or in combination with low-dose diazepam resulted in an increase in cortical TNF-α, IL-1β, NGF, and BDNF levels and a decrease in hippocampal levels and mortality rate after PTZ-induced kindling (52). Decreased hippocampal IL-1β levels prevent epileptogenesis (53, 54), which may be via boosting the GABAergic system (55) and the diazepam effect. Increased TNF-α, IL-1β, NGF, and BDNF levels in the cortex may be in contrast with anti-epileptogenesis. Therefore, additional research should concentrate on clarifying the mechanism of action of c-tDCS and its interaction with other anticonvulsant medications in order to justify its usage as an adjunctive treatment for epilepsy.

Table 1 summarizes tDCS studies performed on animal subjects to prevent epilepsy.

**Clinical studies**

In a study that was conducted in 2021 on patients with epilepsy, seizures were monitored during the c-tDCS session, and it was found that c-tDCS reduced the mean number of seizures while not worsening seizure duration (although reduced, but not statistically) (56). Also, in patients with refractory focal epilepsy, the efficacy of two active tDCS protocols (20 min daily and 2 × 20 min daily sessions) was studied by Yang et al. A 2-mA current was applied through a cathode positioned over the epileptogenic focus. Seizure frequencies were measured in baseline, treatment (14 days), and follow-up periods. In both active tDCS groups, seizure frequencies were significantly reduced compared to the sham group, and 2 × 20 min sessions per day were more effective than one 20 min-session per day (57). In the case of this study, Zoghi and Jaberzadeh mentioned that when tDCS is used therapeutically, it is essential to note that increasing the intensity or duration does not always result in an increase in the expected effect. If parameters are not chosen correctly, the effect may be reversed, and the neurons in the epileptic area may be depolarized instead of hyperpolarized. As a result, the selection of stimulation parameters for novel treatment protocols should be performed more carefully to ensure their efficacy and safety (58).

In one case, a 39-year-old woman with a functional neurological disorder ("psychogenic non-epileptic seizures" or PNES) was successfully treated with positron emission tomography (PET)-guided tDCS. In this case, hypometabolism in the frontal region was detected by the PET scan. PET-guided tDCS (2 mA, 30 min) was performed five days a week, twice a day, and for three consecutive weeks. The anode and cathode were placed respectively on F3 and FP2 frontal regions. PNES and psychogenic involuntary movements decreased after five weeks of treatment. In addition, post-traumatic stress disorder (PTSD), depressive, dissociative, and depersonalization symptoms improved at the same time. The result of this study indicated that PET-scan and tDCS appear to be promising tools for evaluating and treating PNES in clinical practice (59).

Another study assessed the effect of a new symmetric c-tDCS technique compared to sham-tDCS in patients with drug-resistant temporal lobe epilepsy. The anode and cathode were placed over the contralateral homologous region and epileptic focus, respectively. One real session of 1 mA c-tDCS for 20 min was applied to ten subjects. Interictal epileptiform activity was monitored with EEG. Symmetric c-tDCS decreased the percent of the weekly seizure frequency more than sham-tDCS (71% c-tDCS vs. 25% sham) in patients with drug-resistant temporal lobe epilepsy. However, no change in interictal epileptiform activity was found. Most patients who received stimulations experienced only skull itching, and no other side effects were reported (60). Furthermore, a study was conducted to determine the effect of c-tDCS in patients with mesial temporal lobe epilepsy with hippocampal sclerosis, a condition referred to as drug-resistant focal epilepsy syndrome. Patients received 2 mA c-tDCS for 30 min on three consecutive sessions with 24 h intervals. An active electrode was placed over the epileptic hippocampal sclerosis side, and a reference electrode was positioned over the contralateral supraorbital region. The c-tDCS significantly decreased the mean seizure
frequency in patients when compared to their own baseline. After c-tDCS, seizure frequency was reduced by more than 50% in ten patients (83%). In the one-month post-c-tDCS period, six patients (50%) were seizure-free. The findings of this study indicate that c-tDCS may be utilized as an additional treatment option in patients awaiting or refusing epilepsy surgery or even in patients with ineffective surgical results (61). Tekturk et al. examined the effect of c-tDCS on seizure control in another investigation of five patients with Rasmussen’s encephalitis (RE) in another investigation. Cathodal stimulation was applied first, followed by anodal stimulation of the patients. Additionally, three patients received sham stimulation in the final section of the trial. Active electrodes were located over the most affected area, whereas reference electrodes were placed over the contralateral mastoid region. Following cathodal stimulation, the results showed a decrease (more than 50%) in seizure frequency in four patients participating in the experiment. Two patients treated with modulated c-tDCS showed improved outcomes. The longest positive effect persisted for one month. It can be suggested that c-tDCS can be used as an alternative method to improve seizure outcomes in patients with RE, and it would be better to test this method before surgery (62).

In a study, tDCS was utilized to treat a 26-year-old man suffering from symptoms caused by 4-methyl methcathinone (mephedrone). The stimulation protocol included 30 sessions of tDCS (once daily, except on weekends) at 2 mA for 20 minutes. The anode and cathode were respectively placed in the left dorsolateral prefrontal cortex and right supraorbital region. Bilateral electroconvulsive treatment (ECT) was used 22 hours after the last stimulation. However, a case of prolonged seizure duration occurred during ECT following intense prestimulatory treatment with tDCS. This indicates a correlation between prolonged seizure duration and recurrent tDCS treatment before ECT, however, further research is required to confirm this (63).

In a healthy 13-year-old girl, the first generalized tonic-clonic epileptic seizure was observed five days after the second tDCS session. This study applied a-tDCS over the left dorsolateral prefrontal cortex for 20 min with 2 mA intensity. The patient had neither documented history of psychiatric disease nor a familial history of epilepsy or neurological disease. Detailed past medical history indicated that the patient had daily muscle jerks in the lower and upper extremities over the previous two years, which had not been noted in the screening protocol. However, in this case report, the authors noted that tDCS had no causal relation to the first generalized tonic-clonic seizure, especially since the seizure occurred five days after stimulation. According to this report, the presence of muscle jerks must be checked before tDCS stimulation, and a pediatric consultation is also recommended (64, 65). It should be emphasized that the possibility that tDCS increases the risk of seizures cannot be ruled out completely, and additional research is needed in this field.

Figure 1. A schematic diagram depicting possible mechanisms by which tDCS can prevent epileptogenesis. BDNF: brain-derived neurotrophic factor; EEG: electroencephalogram; tDCS: transcranial direct current stimulation.
### Table 2. Overviewing the tDCS effects on seizure control in clinical studies

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<thead>
<tr>
<th>Author/year</th>
<th>Type of study</th>
<th>Epilepsy or seizure type</th>
<th>Sample size</th>
<th>Electrode position</th>
<th>Stimulation protocol</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>San-Juan et al. 2021</td>
<td>Letter to the editor (type of study not specified)</td>
<td>Frequent medically refractory seizures</td>
<td>3 children (5-17 years old)</td>
<td>Cathode over the most active epileptiform region, and anode over the contralateral region</td>
<td>c-tDCS: 2 mA, 30 min per day for 10 days with EEG monitoring</td>
<td>c-tDCS reduced the mean number of seizures without reducing its duration</td>
</tr>
<tr>
<td>Yang et al. 2020</td>
<td>Randomized, double-blind, sham-controlled, and three-arm parallel multicenter study</td>
<td>Refractory focal epilepsy</td>
<td>70 patients (≥ 18 and ≤ 60 years old) active: n = 24, 20 min, active: n = 25, 2 × 20 min, sham: n = 21</td>
<td>Cathode over the epileptogenic focus and reference over a contralateral silent area</td>
<td>c-tDCS: 2 mA, 20 min or 2 × 20 min per day for 14 consecutive days</td>
<td>Seizure frequencies were reduced in both active tDCS groups compared to the sham group, and 2 × 20 min sessions per day were more effective</td>
</tr>
<tr>
<td>Leroy et al. 2019</td>
<td>Case report</td>
<td>Psychogenic non-epileptic seizure (PENS)</td>
<td>A 39-year-old woman</td>
<td>PET guided cathode on FP2 and anode on F3</td>
<td>2 mA, 30 min, 5 days a week, twice a day, for 3 weeks</td>
<td>Decreased PENS and psychogenic involuntary movements, and improved post-traumatic stress disorder (PTSD), depressive, dissociative and depersonalization symptoms</td>
</tr>
<tr>
<td>Assenza et al. 2017</td>
<td>Double-blind, randomized, sham-controlled, crossover, monocentric study</td>
<td>Drug-resistant temporal lobe epilepsy</td>
<td>10 patients (42 ± 15.7 years old)</td>
<td>Cathode over the epileptic focus and anode over the contralateral homologous region</td>
<td>c-tDCS: 1 mA, 20 min, and sham-tDCS: 10 s, on day 25 and day 38.</td>
<td>Symmetric c-tDCS decreased the weekly percentage of seizure frequency more than sham-tDCS (71% vs. 25%) with no change in interictal epileptiform activity</td>
</tr>
<tr>
<td>Tekturk et al. 2016</td>
<td>Randomized cross-over study</td>
<td>Mesial temporal lobe epilepsy with hippocampal sclerosis</td>
<td>12 patients (35.42 ± 6.96 years old)</td>
<td>Active electrode over epileptic hippocampal sclerosis regions (temporal region, either T3 or T4 electrode place) and reference electrode over the contralateral supraorbital region</td>
<td>c-tDCS: 2 mA 30 min, and sham-tDCS: 60 s, for 3 consecutive days</td>
<td>c-tDCS decreased mean seizure frequency in patients compared to the baseline. In ten patients, c-tDCS reduced seizure frequency by more than 50%. Six patients were seizure-free one month post-c-tDCS.</td>
</tr>
<tr>
<td>Tekturk et al. 2016</td>
<td>Descriptive study of a small case series</td>
<td>Rasmussen encephalitis with atrophy and epilepsy partialis continua</td>
<td>5 patients (median age: 19 ± 7)</td>
<td>Active electrodes over the mostly affected area, and reference electrode s over the contralateral mastoid region</td>
<td>Cathodal and then anodal stimulation: 2 mA, 30 min for 3 consecutive days (for non-sham stimulations) and finally sham stimulation (with two-month intervals)</td>
<td>c-tDCS reduced seizure frequency in all but one patient (&gt; 50%). Modulated c-t-DCS had better results in two patients. The longest positive effects lasted for one month. The second modulated a-tDCS and third sham trials were no effective.</td>
</tr>
<tr>
<td>Gezels et al. 2021</td>
<td>Case report</td>
<td>A motivational symptoms induced by mephedrone</td>
<td>A 26-year-old man</td>
<td>Cathode over the right supraorbital region and anode over the left dorsolateral prefrontal cortex</td>
<td>c-tDCS: 2 mA, 20 min, 30 sessions (once daily, except weekends) and finally, 9 sessions of bilateral electroconvulsive therapy (ECT)</td>
<td>A case of prolonged seizure duration occurred during ECT following intense pre-stimulatory treatment with tDCS</td>
</tr>
<tr>
<td>Sierawska et al. 2020</td>
<td>OPTI-Stim study (phase-I randomized double-blind)</td>
<td>Healthy children and teenagers</td>
<td>10 - 18 years old</td>
<td>The left dorsolateral prefrontal cortex</td>
<td>The a-tDCS</td>
<td>Using tDCS, one female participant (a 13-year-old girl) experienced epileptic seizures</td>
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</table>
In this regard, a case study warned about the use of tDCS and the possibility of seizure occurrence. At a pediatric neurology clinic, a 4-year-old boy with left dominant spastic tetraparesis was referred for tDCS treatment to alleviate spasticity and improve upper limb function. For this purpose, 20 min of anodal stimulation (1.2 mA) was applied to the right motor cortex. The patient had no seizures after the first two stimulations, but a seizure occurred four hours following the third stimulation. This study suggested antiepileptic medication changes or anodal stimulation as probable causes of tDCS-induced seizures (66).

In a double-blind clinical study, 20 drug-resistant focal epileptic patients were randomly selected and divided into two treatment and sham groups. The seizure-onset zone was targeted by 2 mA high-definition c-tDCS as a treatment group for 30 minutes for ten days in two weeks. The c-tDCS decreased seizure frequency and interictal epileptiform discharge up to two months after stimulation. It improved life quality as well (67).

Table 2 summarizes tDCS studies performed in human subjects to prevent epilepsy. Figure 1 represents the overall anti-epileptogenesis effects of tDCS.

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Patient Characteristics</th>
<th>Treatment Details</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Splitterbger et al. 2020</td>
<td>Case report</td>
<td>No known history of neurological or psychiatric disease</td>
<td>A 13-year-old girl</td>
<td>The left dorsolateral prefrontal</td>
</tr>
<tr>
<td>Ekici et al. 2015</td>
<td>Case report</td>
<td>Left dominant spastic tetraparesis</td>
<td>A 4-year-old boy</td>
<td>The right motor cortex</td>
</tr>
<tr>
<td>Rezakhani et al. 2022</td>
<td>Randomized parallel and double-blind clinical trial</td>
<td>Drug-resistant focal epilepsy</td>
<td>20 patients (10 treatment and 10 sham)</td>
<td>The seizure-onset zone</td>
</tr>
</tbody>
</table>

CONCLUSION

Generally, if the tDCS efficacy in seizures is recapped, it seems that it prevents epileptogenesis. The c-tDCS can decline neuron spikes and brain waves frequency, as well as hippocampus BDNF expression and IL-1β and can suppress epileptic seizures. The c-tDCS prevents GABAergic decline in the motor cortex leading to a reduction of motor complications. Furthermore, c-tDCS improved cognitive performance. When tDCS is associated with proper instruments, such as PET scans, it will have better outcomes, such as improvement in PTSD, depression, and depersonalization symptoms. Even c-tDCS can be helpful for drug-resistant temporal lobe epilepsy and can prevent surgery. A combination of c-tDCS and pharmaceutical therapeutics can improve epilepsy treatment. If utilizing tDCS, its side effects should be considered; for instance, the c-tDCS increased the TNF-α, IL-1β, NGF, and BDNF levels in the neurons of the brain cortex. In some apparently healthy cases, a-tDCS may disclose epilptic seizures. It is unclear whether tDCS revealed the seizure or induced it; some cues, such as muscle jerks, in such persons should be considered before tDCS. It seems that in this area, the number of studies and the number of patients is small, so further research on a larger number of respondents would help to make better conclusions.

Conflict of interest

There is no conflict of interest. No financial support received.
References


Efekat transkranijalne stimulacije direktnom strujom na kontrolu napada i prevenciju epilepsije

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SAŽETAK

Uvod. Epilepsija je jedna od najčešćih neuroloških bolesti. To je nekontrolisana neuronska aktivnost različitih delova mozga koja dovodi do konvulzija i/ili nesvestice. Iako je u kontroli epileptičkih napada i terapije ostvaren značajan napredak, od 20% do 30% pojedinaca i dalje ima nekontrolisane napade. Neželjeni efekti i komplikacije javljaju se i kod bolesnika čija je terapija pod nadzorom lekara. Oboleli od epilepsije nailaze na mnoštvo različitih izazova. Transkranijalna stimulacija jednosmernom strujom (engl. tDCS) predstavlja bezbednu i neinvazivnu metodu stimulacije mozga koja se primenjuje kod napada i epilepsija otpornih na lekove. Ova metoda prenosi pozitivnu/negativnu električnu struju ka dubljim delovima mozga, moduliraći njihovu električnu aktivnost.


Zaključak. U studijama se ističe da ova metoda verovatno može biti pomoćna metoda u prevenciji i lečenju napada. Kako su u nekim studijama epileptični napadi bili indukovani i potvrđeni nakon primene tDCS-a, ovu metodu treba primenjivati obzirivo.

Ključne reči: napad, konvulzija, prevencija, epilepsija, tDCS