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30.1 Introduction

The rise of interest in neuromodulation is particularly relevant in epilepsy, in which seizures are resistant to pharmacotherapy in approximately one-third of cases, a rate that has not changed despite the introduction of more than 20 new antiepileptic drugs in the late twentieth and early twenty-first centuries [1]. Accordingly, neurostimulation protocols are emerging as potentially valuable tools for seizure control.

Stimulating the nervous system with electricity to treat neuropsychiatric symptoms, seizures included, is not new. In the first century AD, the Roman physician, Scribonius Largus, documented treating headaches by applying electric torpedo fish to the head, and another Roman physician, Pedanius Dioscorides, in 76 AD applied

the torpedo fish to a patient with epilepsy [2]. As brain stimulation in general, neuromodulation for epilepsy has advanced considerably in recent years. Neurostimulation protocols can be coarsely divided into either invasive or noninvasive. Invasive options include vagus nerve stimulation (VNS), deep brain stimulation (DBS), and responsive neurostimulation (RNS). Noninvasive protocols include trigeminal nerve stimulation (TNS), repetitive transcranial magnetic stimulation (rTMS), and transcranial direct current stimulation (tDCS).

30.2 tDCS in Epilepsy

Applied to the mammalian cerebral cortex, tDCS induces both acute and sustained changes in cortical excitability. After a short exposure time to a single session (e.g., 20–30 min), cathodal tDCS typically leads to a reduction in cortical excitability, while anodal tDCS usually increases cortical excitability. Beyond the neocortex, experimental in vitro DC stimulation (DCS) indicates a potential for similar modulation of excitability in the hippocampus [3–5]. In epilepsy, the capacity of cathodal tDCS to reduce cortical excitability has prompted research into this technique's potential in controlling clinical seizures [6, 7].

The relatively low intracranial currents and the absence of directly triggered neuronal action potentials associated with tDCS likely account

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for its favorable safety profile. In contrast to other noninvasive neurostimulation techniques like rTMS, seizures have not been directly associated with tDCS in humans. Currently, five cases of seizures arising during active tDCS have been reported in epilepsy clinical trials, all of which occurred in drug-resistant patients that had events with typical duration and intensity, pointing to a probable coincidental association [8, 9]. The remaining side effects are usually mild and largely limited to skin discomfort and irritation at the electrode sites [10, 11].

30.3 Clinical Studies

Objective changes in cortical excitability as detected by various methods both in humans and animal models have led investigators to implement tDCS interventions for the management of epilepsy with several trials that were undertaken in the past 15 years. In a review of published clinical data in epilepsy through 2020, Sudbrack-Oliveira and colleagues (unpublished data) identified interventions performed in 328 individual patients where 259 were participants in randomized clinical trials (RCTs) and 69 were divided between uncontrolled studies and case series/reports.

tDCS clinical trial results, while still inconclusive, are overall encouraging. In the first human RCT, adults ($N = 19$; average age 24 years) with medically refractory epilepsy secondary to malformations of cortical development were subjected to 1 mA cathodal tDCS delivered in a single session for 20 min using surface sponge electrodes (35 cm^2) arranged with the cathode over the seizure focus and the anode over the region with either normal EEG or the least frequent epileptiform abnormalities in case of multifocal epilepsy. In the sham control condition, the device was turned off after 5 s to generate the similar initial itching sensation without any current delivery for the remainder of the stimulation period. Clinical seizures were monitored by seizure diaries. Electrographic abnormalities were measured by 20-min EEGs obtained at baseline, as well as immediately after, 15 days,

and 30 days after stimulation. EEG readers were blinded to the treatment condition. The results indicate that cathodal tDCS was safe and well tolerated in this population. The frequency of interictal epileptiform discharges was reduced by 64% immediately after tDCS. A favorable trend toward seizure reduction (44% in the treatment group vs. 11% in the control group) was detected, but significant differences in clinical seizure frequency (SF) between treatment and control groups were not identified. Notably, the electrographic response and the trend toward seizure reduction lasted as long as 1 month in some patients [12].

In a study of pediatric patients with refractory focal epilepsy ($N = 36$), children (6–15 years old) received a single session of sham tDCS or verum cathodal 1 mA tDCS for 20 min. tDCS in this study was also administered via a 35 cm^2 sponge cathodal electrode placed over the 10–20 EEG defined epileptogenic irritative zone and the reference anode placed on the contralateral shoulder. While the treatment group received the current for 20 min, in sham stimulation, the current was discontinued just after 30 s in a blinded setting. Epileptiform discharges (spikes and sharp waves) per 30 min of EEG recording at baseline and at different endpoints (15 min, 24 h, 48 h, and 4 weeks) were compared. EEG readers in this study as well were blinded to the treatment condition. The results indicate that tDCS was well tolerated and associated with a significant 50% decrease in EEG epileptiform abnormalities at 24 h and 58% at 48 h after active stimulation. Moreover, a statistically significant, but small decrease of 5% in the clinical seizure frequency was observed in the verum tDCS group with no difference in sham-treated group [11].

Following initial studies that delivered single continuous cathodal tDCS sessions, Zoghi and colleagues undertook a parallel RCT in a sample of patients with temporal lobe epilepsy ($N = 29$, average age 38 years) with a protocol that consisted of two bouts of a 9-min-long stimulation spaced by an interval also during 9 min. This intervention was delivered in a single day, with the cathode positioned in the scalp above the affected temporal lobe and anode positioned at the contra-

lateral supra-orbital area (current = 1 mA, electrode area = 12 cm²). The investigators observed that active stimulation was associated with a greater reduction in seizure frequency at 1-month follow-up (42.14% SF reduction in active tDCS and 16.98% reduction in sham group). However, this study has some issues: baseline seizure frequency assessment was based on participant's recollection and six patients did not return their seizure diaries following the intervention, which might have influenced the results. Interestingly, authors used short interval intracortical inhibition (SICI) as detected by paired-pulse transcranial magnetic stimulation (pp-TMS) as a surrogate measure of cortical excitability. They observed that inhibitory activity in the primary motor cortex was increased in the experimental group as compared to the sham arm [13].

Two other RCTs have investigated the effects of tDCS interventions in patients with temporal lobe epilepsy, in this case secondary to hippocampal sclerosis, both delivering repeated stimulation sessions. In the first study, which had a crossover design ($N = 12$, average age 35 years), Tekturk and colleagues delivered three 30-min sessions of either active or sham tDCS over consecutive days. The second bout of three sessions was separated from the first by a washout period of 60 days. The intervention, as done by prior investigators, had a montage with cathode placed in the scalp region overlying the affected temporal lobe and the anode at the contralateral supraorbital area (current = 2 mA peak to peak, electrode area = 35 cm²). However, instead of delivering stimulation at a fixed intensity, the intervention consisted on what authors called modulated tDCS, characterized by a sinusoidal fluctuating current. The chosen frequency for the stimulation was 12 Hz, in the upper alpha range, aimed to restore abnormal brain activity with this physiologic rhythm based on results from neurofeedback studies. Results showed a 84% decrease in SF at 1-month follow-up after active tDCS as compared to no change following the sham treatment [14]. In the second study, San-Juan and colleagues randomized 28 participants also with a diagnosis of hippocampal sclerosis (average age 38 years) to one of three treatment

arms: active tDCS consisting of either three or five 30-min sessions (current = 2 mA, electrode area = 35 cm²) delivered once in consecutive days or sham/placebo. As usual, the cathode was positioned over the affected temporal lobe and anode at the contralateral supraorbital area. Active stimulation was associated with a significant decrease in seizure frequency at 2-month follow-up (43.4% and 54.6% SF reduction for 3 and 5 sessions, respectively). EEG epileptiform activity was also quantified, but it was similarly reduced in active and sham groups [8].

In the largest RCT so far, Yang and coworkers investigated the effectiveness of an intensified tDCS protocol on seizure frequency in a sample of patients with drug-resistant focal epilepsy of varied etiologies ($N = 70$, average age 31 years). Participants were randomized to one of two active tDCS protocols or sham stimulation. The intervention consisted of 14 consecutive days of stimulations (current = 2 mA, electrode area = 11.9 cm²) delivered once a day during 20 min in one active arm and twice a day (totalizing 40-min session daily) in the second active group. The cathode was as well positioned in the scalp area with most abnormal EEG findings and the anode at a contralateral "silent" area. Both active groups presented a significant decrease in SF when compared to the sham group, a decline that was more pronounced with the more intense protocol (50.73–21.91% and 63.19–49.79% weekly SF reduction for 20-min and 40-min stimulation, respectively). Furthermore, the intensified protocol was associated with a longer duration of the effects (5 weeks as compared to 4 weeks for 20-min stimulation) [9].

The single RCT that performed tDCS interventions in a sample not solely composed by participants with focal epilepsy was undertaken by Auvichayapat and colleagues. In that study, 22 children (average age 6.5 years) diagnosed with Lennox-Gastaut Syndrome (LGS), a condition characterized as combined focal and generalized epilepsy, were randomized to either sham or active stimulation. Sessions lasted 20 min and were delivered once through 5 consecutive days. This study was also unique in relation to electrode montage, with the cathode positioned at

C3 (close to the left primary motor area) in all patients and the anode at the right shoulder (current = 2 mA, electrode area = 35 cm²). Results showed a 89.75% reduction in daily SF in the active group at 1 week with a gradual loss of the effects observed up to 1-month follow-up (55.96% reduction) [15].

In addition to seizure suppression, tDCS may have a role in mitigating behavioral symptoms that are commonly comorbid with epilepsy. In a recent pilot study of 33 adults with controlled temporal lobe epilepsy, Liu and colleagues explored the tDCS effects on depression and memory dysfunction [16]. Two mA, 20-min tDCS was delivered for 5 days with anode over the left dorsolateral prefrontal cortex and cathode over the right supraorbital area. While the active treatment group received current for 20 min, the current during sham control stimulation was ramped up only for 30 s and thereafter ramped down. The 5-day tDCS course corresponded to a modest improvement in depressive symptoms immediately after active treatment. Notably, investigators did not find an increase in interictal discharge frequency thus indicating tDCS safety for applications other than seizure suppression in patients with epilepsy.

30.4 Preclinical Studies

The mixed outcomes of human tDCS trials in epilepsy underscore the need for preclinical studies that may inform future clinical tDCS study design. Notably, as the term “transcranial” is not relevant for in vitro brain stimulation, “DCS” rather than “tDCS” is often used to describe the stimulation condition in preclinical studies.

Preclinical DCS research can provide insight into the mechanism by which DCS may produce a sustained antiepileptic effect. This was recently addressed by Chang and colleagues who studied the cathodal DCS effect on acute chemoconvulsant in isolated mouse thalamocingulate brain slices, an in vitro model of frontal lobe epilepsy. In their experiment, brain slices were stimulated by two parallel Ag/Ag-Cl electrodes connected to an isolated stimulator placed external

to the slice in a recording chamber to generate a uniform electric field (4 mV/mm). Spontaneous excitatory postsynaptic currents (EPSCs) were recorded, as were epileptic EPSCs induced by bath application of either the potassium channel blocker 4-aminopyridine or the GABA_A receptor antagonist bicuculline. Consistent with the past studies, cathodal DCS suppressed evoked synaptic transmission and spontaneous EPSCs, a finding that the authors attributed to real-time neuronal membrane hyperpolarization. However, the antiepileptic effect persisted in this model, and was shown to be dependent on activation of the n-methyl-d-aspartate (NMDA) type glutamate receptor, thus behaving in ways like the well-described phenomenon of NMDA-dependent long-term depression (LTD) of excitatory synaptic strength [17]. The value of such data is an identification of a molecular pathway by which DCS may suppress seizures. This not only satisfies a scientific curiosity but also offers an opportunity to test whether pharmacotherapy that facilitates a component of this pathway may also facilitate the antiepileptic efficacy of tDCS, which, as above, is incomplete in clinical practice. However, systematic in vitro studies that investigate the molecular substrate of the DCS antiepileptic effect are rare. More commonly, in vitro DCS data provide insight into the electrophysiologic basis of seizure suppression by tDCS. For instance, early in vitro studies in a low-calcium hippocampal slice model identified that epileptiform discharges may be suppressed by field strengths in the 1–5 mV/mm range and that such suppression is polarity dependent [18, 19].

Among the more specialized applications that can be tested in animal epilepsy models is the capacity for cathodal tDCS, applied as a pretreatment to prophylax against seizures. This was first tested by Liebetanz and colleagues in a modified cortical ramp-stimulation focal seizure model in rats. In these experiments, tDCS was delivered with unilateral epicranial conductive electrodes to rat sensorimotor cortex, and threshold for localized seizure activity was determined by trains of pulsatile stimulation (50 Hz; 2 ms; 2 mA) delivered through the same epicranial

contact. One group of animals received cathodal tDCS (100 μ A) for 30 and 60 min or anodal tDCS for 60 min. In another group, the current intensity was doubled (200 μ A) and stimulation durations were halved in all three conditions. The main finding of the work was that cathodal tDCS caused an elevation of localized seizure threshold lasting for ≥ 2 h. In contrast, anodal tDCS had no significant effect on seizure threshold, confirming *in vivo* a polarity-dependent anticonvulsant tDCS effect, and the absence of seizure exacerbation by anodal stimulation, as suggested also by clinical tDCS trials [20].

In complement to the preclinical study of tDCS in focal seizures [20], the antiepileptic potential of cathodal tDCS was also demonstrated in a rat amygdala-kindling temporal lobe epilepsy model. Here, Kamida and colleagues demonstrated that cathodal tDCS reduced clinical seizure severity and EEG after discharge duration, while elevating the after discharge threshold, and these effects lasted at least 1 day after the last tDCS session (30-min daily treatment at 200 μ A for 1 week). This treatment regimen also corresponded to improved cognitive performance on the Morris water maze [21]. The same group also investigated the effects of cathodal tDCS on convulsions in a rat pup lithium-pilocarpine status epilepticus model. In this study, rats were treated for 2 weeks with 200 μ A cathodal tDCS delivered for 30 min per session using epicranial electrodes. Monitored over 2 weeks post stimulation, the authors found a significant 21% reduction in the frequency of convulsions between sham and cathodal tDCS treated rats suggesting an antiepileptic effect. Among other findings, long-term treatment with cathodal tDCS also had neuroprotective effects on the rat hippocampus and led to improvements in performance of the water maze spatial memory task [22].

The above data indicate an intriguing prospect for tDCS as a means to interfere with epileptogenesis, rather than just seizures. The search for an effective and safe antiepileptogenic treatment is an active field in experimental epilepsy. The unmet need for such treatment is underscored by complete absence of clinical antiepileptogenic interventions: For instance, none of the approxi-

mately 40 drugs that are prescribed to treat seizures are antiepileptogenic. Thus, further studies of tDCS in its capacity to prevent the onset of epilepsy after an epileptogenic brain injury such as trauma, stroke, or status epilepticus are necessary.

In contrast to *in vivo* experiments that tested a delayed antiepileptic tDCS effect, in a study by Dhamne and colleagues, cathodal tDCS was tested in the acute seizure setting that approximates status epilepticus to assess an immediate anticonvulsant effect. In this experiment, investigators modeled the realistic scenario that seizures will have already started by the time tDCS is deployed in the clinical arena. Moreover, a patient with status epilepticus will be likely to have received an anticonvulsant before the start of tDCS. Cathodal tDCS in this experiment was delivered via a scalp electrode for 20 min at either 1 mA, 0.1 mA, or, in the control condition, 0 mA. And to simulate a likely clinical combination, tDCS was also tested in combination with lorazepam, a first-line anticonvulsant benzodiazepine that is routinely administered to human patients with status epilepticus. The results identify electrographic seizure suppression within minutes of 1 mA cathodal stimulation. Moreover, a combination of tDCS and a subeffective lorazepam dose suppressed seizures better than either intervention alone, suggesting that cathodal tDCS may act synergistically with lorazepam [23]. Of translational relevance for future clinical application, these data indicate an important direction for neuromodulation research toward systematic testing of combination drug-device therapy in epilepsy.

30.5 Conclusions

Given that the rate of drug-resistant epilepsy has not changed much in recent years, tDCS offers a plausible noninvasive and nonpharmacologic option to improve seizure control in patients with intractable seizures, particularly when surgical intervention has either failed or is not an option. Most RCTs so far indicate that tDCS is an effective intervention regarding seizure control, with

measurable effects being detected up to 2 months after the end of the stimulation sessions. However, tDCS antiseizure effects as well as its influence on surrogate markers of cortical excitability have yet to be substantiated and replicated in larger clinical trials. Additionally, further work should address samples other than patients with drug-resistant focal epilepsies (e.g., generalized epilepsy, status epilepticus). Nonetheless, tDCS's promising clinical effects in addition to a benign side-effect profile suggest a favorable risk: benefit ratio and high likelihood of near-future implementation in clinical epilepsy. The inconsistent findings with respect to seizure suppression in some trials underscore the need for improved patient-specific protocols that enable superior targeting of the epileptogenic foci/networks [24–26]. Last, novel neuroprotective and antiepileptogenic tDCS applications are suggested by preclinical research, and also may lead to disease-modifying treatment strategies in future clinical embodiments of this technology.

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