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# Cathodal tDCS and HD-tDCS Neuromodulation Technique in the Treatment of Patients with Drug-resistant Epilepsy

Review

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## Abstract

Cathodal transcranial Direct Current Stimulation (ctDCS) is a safe, non-invasive neuromodulation method that has been investigated for the management of epilepsy over the past three decades, primarily to reduce seizure frequency. The advanced version of transcranial Direct Current Stimulation (tDCS), High-Definition tDCS (HD-tDCS), has been developed to provide increased focality and to reduce neuromodulatory effects beyond the epileptogenic area of interest; therefore, it is preferred over traditional tDCS. Findings from animal studies, human research, and clinical trials suggest that ctDCS and HD-tDCS may suppress seizures in patients with drug-resistant focal epilepsy (DRFE).

This review aims to analyze and synthesize clinical studies and research articles to provide a deeper understanding of the potential of HD-tDCS in managing seizures among patients with DRFE. The application of optimized HD-tDCS appears to reduce seizure frequency effectively in most DRFE cases. However, some patients experienced an increase in seizure frequency for reasons that remain unclear and warrant further investigation.

**Keywords:** HD-tDCS, Drug-resistant epilepsy, Brain stimulation, Patient personalization treatment.

## 1. INTRODUCTION

Epilepsy, a neurological disorder characterized by recurrent seizures, affects over fifty million individuals worldwide (Mbizvo, Bennett, Simpson, Duncan, & Chin, 2019). In addition to the seizures themselves, individuals with epilepsy often experience neurocognitive impairments and adverse side effects from antiepileptic drugs. Drug-resistant epilepsy (DRE) presents significant challenges, leading to a markedly reduced quality of life for affected individuals. Surgical intervention is considered an option for only about 5% of patients with DRE. Alternative treatments such as deep brain stimulation (DBS) and vagal nerve stimulation (VNS) are available; however, these approaches require invasive surgical procedures. In contrast, transcranial Direct Current Stimulation (tDCS) offers a non-invasive, cost-effective alternative (Jehi, Silveira, Bingaman, & Najm, 2010). Numerous studies have explored the potential benefits of tDCS, suggesting its efficacy not only in managing seizures but also improving outcomes for patients with neurodegenerative diseases, motor dysfunctions, and cognitive impairments (Fregni et al., 2020; Fritsch et al., 2010). Consequently, tDCS has emerged as a promising therapeutic method for drug-resistant epilepsy.

This technique involves the application of weak direct currents, typically ranging from 1–3 mA, delivered through surface electrodes placed on the scalp, specifically an anode and a cathode (Nitsche & Paulus, 2009), as illustrated in Figure 1. Traditional tDCS devices utilize two electrodes, with the stimulation classified as cathodal or anodal depending on the configuration of the electrodes and the desired therapeutic effect.

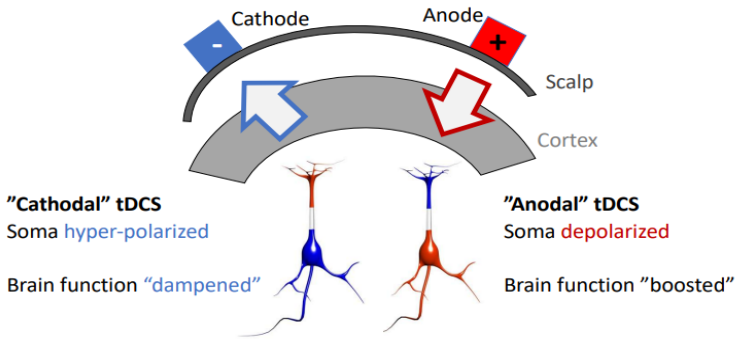


**Figure 1.** Schematic diagram illustrating anodal and cathodal tDCS mechanism (Radman et al., 2009)

The underlying hypothesis of cathodal or anodal tDCS is that the behavioral or neurophysiological effects observed reflect either inhibition or excitation of brain regions near the cathode or anode, respectively (Garnett et al., 2015). As illustrated in Figure 1, electric current enters the body through the anode and exits through the cathode (Biabani et al., 2017). In cases where the goal is to inhibit brain activity, cathodal tDCS (ctDCS) is applied, whereas anodal tDCS is used when the aim is excitation.

High-Definition tDCS (HD-tDCS) differs from traditional tDCS by employing more than two electrodes. For example, a three-electrode montage may include one anode with two cathodes or one cathode with two anodes. In general, a system with $n$ electrodes allows multiple stimulation configurations determined by combinatorial arrangements. A critical requirement in any HD-tDCS setup is ensuring that the total current delivered through the anode(s) equals the total current drawn through the cathode(s) (Dmochowski et al., 2011). Electrode placement typically follows the 10/10 or 10/20 electroencephalography (EEG) systems.

For the purposes of this review, the cathode is positioned over the epileptogenic zone, with anodes placed around it to facilitate ctDCS. The central hypothesis for using tDCS in epilepsy treatment is that personalized electrode configurations are essential for achieving the desired outcomes. This is particularly relevant given that most epilepsy patients have a distinct, unilateral seizure onset site, despite the potential for bilateral interictal spikes (Sudbrack-Oliveira et al., 2021; San-Juan, Sarmiento, Márquez-González, & Barraza, 2018). In contrast, the use of smaller electrodes in HD-tDCS enhance current intensity and spatial precision enabling for targeted stimulation of specific brain areas (Edwards et al., 2013). HD-tDCS therefore provides more focal effects and is preferred in certain clinical applications. Early human studies have confirmed the safety of HD-tDCS as a neuromodulation technique (Borckardt et al., 2012). Additionally, several studies have demonstrated its effectiveness in improving pain management, motor function, working memory, and verbal learning (Borckardt et al., 2012; Villamar et al., 2013; Nikolin, Loo, Bai, Dokos, & Martin, 2015; Caparelli-Dáquer et al., 2012; Donnell et al., 2015). Specifically, current can be directed to targeted brain regions—such as the parietal and temporal association areas—to stimulate or modulate circuits that are thought to have antiepileptogenic properties or that serve as key nodes within epileptogenic networks.

### *1.1 Brief chronological history*

A brief historical overview is essential for understanding the development of advanced methods such as transcranial direct current stimulation (tDCS) and high-definition tDCS (HD-tDCS). The therapeutic use of electrical stimulation began in the 1960s, when researchers first observed that anodal currents could enhance neuronal excitability, whereas cathodal stimulation produced inhibitory effects. Early studies investigating the potential of direct current to modulate neuronal behavior, including seminal work by Bindman et al. (1964) and Nitsche & Paulus (2000), established the foundation for its later applications in treating conditions such as epilepsy. Over time, technological advances have led to the development of HD-tDCS, which utilizes smaller electrodes for more precise stimulation, offering enhanced focality compared to traditional tDCS methods. By comparing these innovative techniques with conventional approaches, we can better understand their relative advantages and limitations, ultimately leading to improved treatment strategies for neurological disorders like drug-resistant epilepsy. This historical context underscores both the progress made in neurostimulation therapies and the ongoing need for innovation in the field.

## 2. DISCUSSION

This paper aims to examine the mechanisms and effects of HD-tDCS and traditional tDCS in the context of drug-resistant focal epilepsy (DRFE). A comprehensive review of the literature is provided, focusing on key findings, methodologies, and challenges associated with these advanced neurostimulation techniques. By synthesizing various studies, we seek to clarify how tDCS and HD-tDCS may modulate neuronal excitability and offer therapeutic benefits for patients with epilepsy.

Following a discussion of the fundamental mechanisms of action of tDCS and HD-tDCS, an overview of their clinical applications in the treatment of DRFE is presented. This section is followed by an exploration of the neurological mechanisms underlying cathodal tDCS (ctDCS) and its integration with cutting-edge imaging technologies such as electroencephalography (EEG) and functional magnetic resonance imaging (fMRI). We then review current evidence regarding the efficacy and safety of optimized cathodal HD-tDCS (cHD-tDCS). Finally, we highlight the importance of personalized electrode configurations in optimizing treatment outcomes. Through this systematic approach, the paper aims to provide a coherent framework for understanding and evaluating the clinical implications of these innovative neurostimulation methods in epilepsy management.

### *2.1. Mechanism of action of tDCS and HD-tDCS*

Transcranial direct current stimulation (tDCS) exerts neuro-modulatory effects by delivering a constant current with a specific waveform to the scalp. The type of stimulation is determined by the polarity of the constant current waveform (Beumer et al., 2022). Research has shown—particularly in animal studies (Nitsche & Paulus, 2000; Philip et al., 2017)—that anodal tDCS induces neuronal depolarization and increases neuronal excitability, whereas cathodal tDCS (ctDCS) produces the opposite effect, leading to neuronal hyperpolarization and reduced excitability.

In contrast, cathodal tDCS (ctDCS) produces the opposite effect, leading to neuronal hyperpolarization and a decrease in neuronal excitability. It is important to note that the excitatory effect of anodal stimulation is highly dependent on electrode placement. Significant neuronal excitation has been predominantly observed when the anode is placed over the motor cortex and the cathode on the contralateral forehead. This finding emphasizes the critical role of electric-field interactions with neuronal geometry in determining the effectiveness of anodal stimulation.

The post-stimulation effects of tDCS are influenced by several parameters, including current intensity, stimulation duration, and the radial electric field generated during stimulation (Seo & Jun, 2019). In animal studies, longer stimulation durations have been associated with more prolonged effects (Nitsche & Paulus, 2000). Fertonani, Pirulli, and Miniussi (2011) proposed a stimulation-dependent electrophysiological model to better explain these mechanisms. According to this model, cathodal stimulation induces hyperpolarization by decreasing the rate of neuronal depolarization, whereas anodal stimulation facilitates neuronal depolarization.

Moreover, electrical stimulation can simultaneously influence populations of neurons, increasing their membrane potentials and producing depolarization. These mechanisms, occurring near neuronal membranes, help explain how tDCS can modulate—and in some cases enhance—cortical function (Silvanto, Muggleton, & Walsh, 2008).

High-Definition-tDCS (HD-tDCS) is characterized by the use of smaller electrodes, known as HD electrodes (Minhas et al., 2010). These electrodes are typically made of small circular Ag/AgCl (silver/silver chloride) materials and are separated from the skin by a gel contained within a plastic cylinder (Villamar et al., 2013). The plastic cylinder helps control the distance between the electrode and the skin (Truong & Bikson, 2018). Due to their reduced size, HD electrodes allow for greater precision in electrode placement, making HD-tDCS particularly effective in targeting specific brain regions with high accuracy (Rawji et al., 2018).

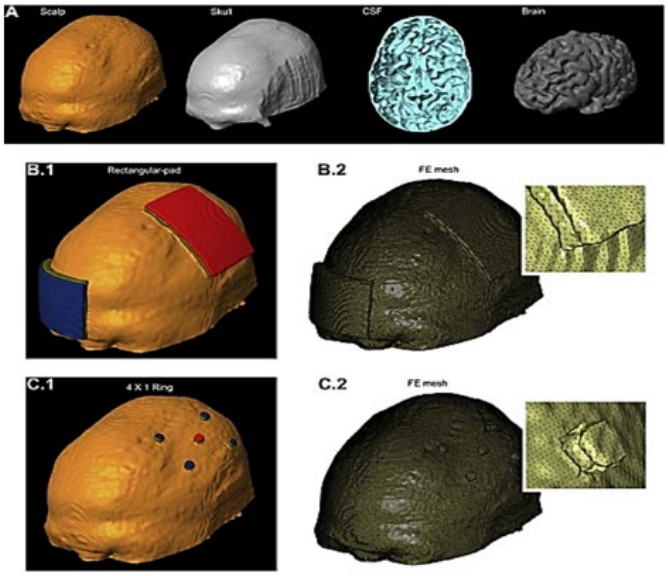


**Figure 2.** HD-tDCS vs conventional tDCS (Datta et al., 2009)

Although the primary focus of this review is on ctDCS and cHD-tDCS, research in this area is limited, particularly with respect to studies involving epileptic patients. To address this gap, we compare findings from studies that examine analogous stimulation techniques. For instance, Datta et al. (2009) conducted a theoretical comparison between anodal tDCS and anodal HD-tDCS, and we discuss their results while attempting to draw inferences for cathodal stimulation based on the practical work of Paula-Faria et al. (2012). Their study highlighted several challenges associated with HD-tDCS configurations. Notably, their results were derived from modeling parameters based on a human brain model, and practical applications may yield different outcomes due to variations between theoretical models and real-world settings.

Figure 2 illustrates the core findings of the study, with Figure 2 (A) displaying segmented compartments in the following order: scalp, skull, cerebrospinal fluid (CSF), and brain. These segments were derived from raw 3T MRI scans, which were then processed into volume conductor models maintaining the same resolution ($1mm^3$) as the MRI data. The setup for the investigation involved two types of transcranial Direct Current Stimulation (tDCS) configurations. Figure 2 (B.1) shows a conventional tDCS setup, where a $7\times5$ $cm^2$ rectangular electrode pad with an anode (active) is placed over the primary motor cortex, with one cathode positioned accordingly. In contrast, Figure 2 (C.1) illustrates a High-Definition tDCS (HD-tDCS) setup, featuring electrodes with a 4mm radius, where one anode (active) is placed over the motor cortex, and four cathodes are positioned at a 3 cm radius from the anode.

The study's observations revealed that the peak electrical field generated by a 1mA conventional tDCS setup (Figure 2 B.1) was equivalent to that of a 2mA HD-tDCS ring configuration (Figure 2 C.1). This finding indicates that, although the current was more diffusely applied in the conventional tDCS configuration, the magnitude of the induced electric field was comparable to that of the 2mA HD-tDCS setup. Furthermore, while HD-tDCS offers enhanced spatial resolution, increasing the surface current does not necessarily result in a corresponding increase in the peak induced cortical electric field magnitude. This is due to the phenomenon of shunting across the skull, where the current does not flow through the brain tissue itself (Marom Bikson et al., 2009). As a result, there is no effective stimulation in these areas, leading to a reduced peak-induced cortical stimulation.

To fully exploit the high spatial resolution of HD-tDCS while maintaining a sufficient peak-induced electric field, it is necessary to increase the surface current to compensate for the current shunted across the skull. However, this increase in surface current may lead to skin irritation due to excessive current density on the scalp. One potential solution is to increase the distance between electrodes, which can help offset the increased surface current. However, this adjustment comes at the cost of reduced focality, as the current becomes more diffuse. Thus, there is an inherent trade-off between achieving greater focality and obtaining a higher peak-induced electric field in the ring configuration shown in Figure 2(C.1). These observations suggest that the ring configuration may provide a reasonable balance, offering both safer and more focal stimulation compared to other configurations.

It is important to note that the study discussed primarily involved anodal tDCS and anodal HD-tDCS configurations, where the anode was the active electrode, and no patients with epilepsy were included in the research. Therefore, further focused investigations are needed to adapt and refine this stimulation technique to improve its focality and efficacy for epileptic patients.

In the work by Paula-Faria et al. (2012), 1 mA of current was delivered using a Phoresor 850 device to four 1.1 $cm^2$ electrodes (one unique cathodal electrode and three adjacent shorted anodes) in a study involving two patients with epilepsy. Although their electrode configuration differed from the ring montage used in the previous study—which likely influenced the outcomes—they still reported positive results in both patients. This suggests that tDCS may be a promising approach for epilepsy treatment, but further optimization and refinement of stimulation parameters are necessary for broader clinical application.

### *2.2. Basic principles of the tDCS and HD-tDCS in drug resistant epilepsy*

In the 1960s, researchers conducted early animal studies on cortical direct current (DC) stimulation and discovered that anodal currents enhance neuronal excitability, while cathodal stimulation has the opposite effect, reducing neuronal activity (Bindman, Lippold, & Redfearn, 1964; Nitsche & Paulus, 2009). In the context of epilepsy, ctDCS is thought to reduce neuronal depolarization at the targeted epileptogenic zone or relay regions, such as the thalamus, thereby decreasing the likelihood of hyperexcitability that could lead to seizures. tDCS is believed to primarily affect pyramidal cells in the cortex, as these neurons are oriented perpendicular to the cortical surface (Fritsch et al., 2010). Pyramidal neurons are modeled as dipoles aligned normal to the cortical surface, and although tangential components of the electric field may stimulate neurons during tDCS, it is mainly the normal component of the electric field that affects them.

It is important to note that exciting epileptogenic regions with tDCS is undesirable, as it could potentially trigger seizures. However, tDCS is generally considered to modulate neuronal excitability without being sufficiently potent to directly induce seizures (Wexler, 2017). Both ctDCS and High-Definition tDCS (HD-tDCS) have shown effectiveness in the treatment of epilepsy, particularly in reducing seizure frequency in patients with drug-resistant epilepsy or epilepsy disorder. This is primarily due to the inhibitory effect of cathodal stimulation on various cortical levels (Masina et al., 2021). ctDCS works by reducing cortical excitability, effectively inhibiting neuronal firing and helping to prevent seizures (Kabakov, Müller, Pascual-Leone, Jensen, & Rotenberg, 2012).

However, despite the promising results, there is no consensus on the optimal placement of the anode in these stimulation protocols. Undesired excitatory stimulation can occur if the anode is placed over a susceptible brain region, potentially diminishing treatment effectiveness or even increasing seizure frequency (Ng et al., 2023). This issue can be mitigated by using HD-tDCS, as it involves surrounding the cathode with multiple anodes, dispersing the anodal current and reducing the risk of unintended excitatory

stimulation. Furthermore, electrode localization strategies have been optimized through computer simulations to maximize current flow to the targeted coordinates while minimizing its spread to unwanted areas (Datta et al., 2009). Additionally, many commercial HD-tDCS devices are now integrated with EEG recording capabilities, allowing for real-time seizure monitoring and facilitating more precise and responsive treatment.

### *2.3. Coupling TES with EEG and fMRI*

A particularly interesting combination is transcranial electrical stimulation (TES) and electroencephalography (EEG), as illustrated in Figure 3. These processes are mirror-symmetric and connected by the well-established reciprocity concept first proposed by (Helmholtz,1853). The significance of the TES-EEG integration for the focus of this review lies in its potential application for obtaining EEG data during a seizure, identifying its focality, and then applying reciprocal focal electrical stimulation. If implemented, this approach could offer more targeted, focal, and potentially more effective treatment, optimizing the therapeutic outcomes for epilepsy management.

The concept of integrating TES with electroencephalography (EEG) has been explored for decades, but no formal framework has been established for matching optimal stimulation parameters to EEG recordings. However, (Dmochowski et al., 2017) advanced this idea by deriving a closed-form equation for the TES configuration that, without making assumptions about the position or distribution of the sources, optimally stimulates the targets identified in the recorded EEG data. This approach, as illustrated in Figure 3 (A) and (B), provides a method for aligning stimulation with the sources identified through EEG. Additionally, they demonstrated a duality between EEG source localization and TES targeting, highlighting that the proposed targeting strategy would fail if the source localization itself were inaccurate. These theoretical predictions were validated by numerical simulations using several head models, which also provided focality and intensity measurements of the achieved stimulation.

Furthermore, the researchers developed a generic formalism for coupling EEG and TES to address the challenge of applying TES currents in a way that effectively targets the source of EEG activation. They developed a closed-form formulation for the TES electrode arrangement, or "montage," that produces an electric field most closely matched to the activation pattern by expressing both the EEG and the TES as linear systems connected by a shared transfer matrix.

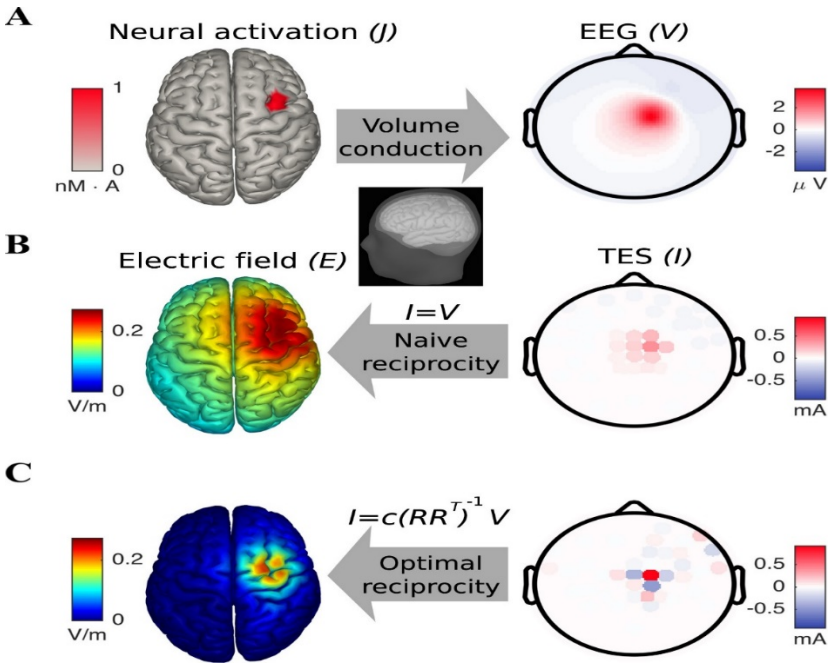


**Figure 3.** EEG usage in tES stimulation for targeting active brain regions, (Dmochowski, Koessler, Norcia, Bikson, & Parra, 2017)

An electric field is directed toward the location of brain activation through reciprocal stimulation. Figure 3 (A) indicates a radially-symmetric pattern of electric potentials appears on the scalp during focal neuronal activation of the right frontocentral cortex, and Figure 3 (B) a diffused electric field is produced by patterning the stimulation currents in accordance with the observed scalp activity, or "naive" reciprocity. This electric field is strong at the point of activation and extends over large sections of cortex. In Figure 3 (C), Focal stimulation at the neuronal activation is obtained by applying TES proportionate to the spatially decorrelated EEG.

It is important to note that the TES coupled with EEG is neither tDCS nor HD-tDCS by definition. The idea is only to apply surface electric current based on the recorded EGG from a specific head region. However, since reciprocal electrical stimulation must equally be focal to the area of activation, it can be inferred that this constitutes an HD-tDCS configuration and may be either anodal or cathodal depending on the desired outcome. Within the scope of this review paper, TES coupled with EEG is therefore considered cHD-tDCS by inference.

Localized inhibition would still be relevant in cases of focal epilepsy related to well-delimited structural lesions. In such cases, neuro-navigation techniques with greater spatial resolution like functional resonance magnetic imaging (fMRI) or transcranial magnetic stimulation coupled with electroencephalography (TMS-EEG) especially when combined with HD-tDCS protocols can boost tDCS localized effects.

### *2.4. Neurological mechanisms of ctDCS*

As mentioned, there are generally more studies on traditional tDCS compared to HD-tDCS, leading to a greater number of ctDCS studies than cHD-tDCS studies for drug-resistant focal epilepsy (DRFE). However, for the majority of patients with DRFE or other forms of chronic epilepsy disorders, both ctDCS and cHD-tDCS have shown effective reductions in seizure frequency rates. Indeed, for ctDCS studies, significant improvements in seizure management and control were observed in the majority of studies

involving both adults and children with focal epilepsy following its application (Yang et al., 2020; Auvichayapat et al., 2013; Zoghi et al., 2016; Yook, Park, Seo, Kim, & Ko, 2011; Assenza et al., 2017; San-Juan et al., 2017; Lin et al., 2018; Fisher et al., 2023). These studies collectively highlight the potential of ctDCS as an effective therapeutic approach for managing focal epilepsy and reducing seizure frequency.

A reduction in seizure frequency following the application of ctDCS was also observed in patients with Lennox–Gastaut syndrome (LGS) (Auvichayapat, Sinsupan, Tunkamnerdthai, & Auvichayapat, 2016), epilepsia partialis continua (Grippe, Brasil-Neto, Boëchat-Barros, Da Cunha, & Oliveira, 2015), Rasmussen's encephalitis (Tektürk et al., 2016; Zoghi et al., 2016), and pharmacoresistant epileptic spasms (Yang et al., 2019). Furthermore, most of the successful ctDCS studies had follow-up durations of less than a year (Yang et al., 2020; Auvichayapat et al., 2013; Zoghi et al., 2016; Assenza et al., 2017; San-Juan et al., 2017; Auvichayapat, Sinsupan, Tunkamnerdthai, & Auvichayapat, 2016; San-Juan et al., 2011; Fregni et al., 2006).

Additionally, recent articles have reported fluctuations in functional connectivity in patients with epilepsy following the application of ctDCS. It is also important to note that one study suggested that tDCS may exert its effects by modulating brain networks as a whole, rather than merely inducing changes in the local activity of the targeted region or area of interest (Simula et al., 2022).

### *2.5. Efficacy and safety of cHD-tTDCs for DRFE*

There are few research studies that have investigated the effects of cHD-tDCS for drug-resistant focal epilepsy (DRFE). One notable study by (Rezakhani et al. 2022) involved a randomized parallel, double-blind clinical trial with 20 patients, which demonstrated that cHD-tDCS led to a reduction in both interictal epileptiform discharges (IEDs) and seizure frequency (SF) in DRFE patients (Rezakhani, Amiri, Weckhuysen, & Keliris, 2022). Additionally, a case study by Meiron et al. reported positive outcomes, such as a reduction in IED levels, in a patient with Ohtahara syndrome (Meiron et al., 2019). Another clinical trial using EEG in 10 patients with drug-resistant epilepsy (DRE) reported positive outcomes, including a decrease in SF and changes in functional plasticity (Daoud et al., 2022). Furthermore, Kaye et al. demonstrated the efficacy of HD-tDCS for DRFE management, with most patients experiencing positive results (Kaye et al., 2021).

However, in two case studies, HD-tDCS failed to reduce seizure frequency (Karvigh, Motamedi, Arzani, & Roshan, 2017; Meiron et al., 2017). Additionally, the follow-up periods for cHD-tDCS in three studies were relatively short, lasting less than one year (Rezakhani, Amiri, Weckhuysen, & Keliris, 2022; Meiron et al., 2019; Kaye et al., 2021). Consequently, more multisite, sham-controlled clinical trials are needed to better assess the utility and long-term effectiveness of cHD-tDCS in the management of DRFE.

### *2.6. ctDCS and HD-tDCS Electrode Montage personalization*

Currently, ctDCS and HD-tDCS techniques for patients with drug-resistant epilepsy are still in the experimental phase, as the optimal treatment protocol to achieve the best outcomes has yet to be clearly defined. However, to attain optimal results for focal brain disorders, such as epilepsy, the development of personalized stimulation protocols is a critical step. Figure 4 illustrates the flowchart for obtaining personalized tDCS based on MRI or EEG recordings, which can help tailor the stimulation to the individual needs of each patient, potentially enhancing the efficacy of these neuromodulation techniques.

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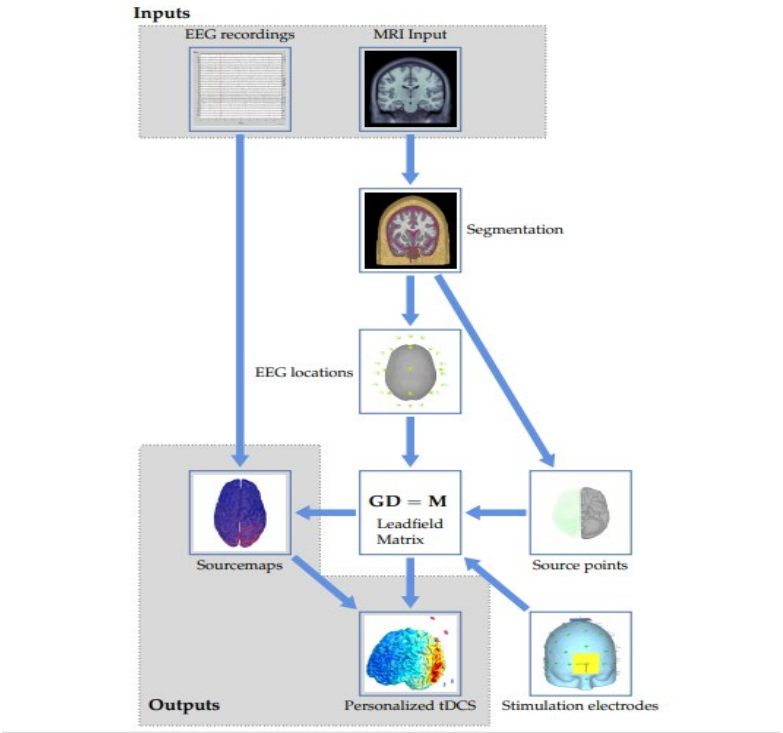


**Figure 4.** Flowchart for obtaining optimized tDCS /HD-tDCS (Beumer et al., 2022)

A personalized model specifically adapts the electrode montage to each patient before the onset of treatment. The first step in personalization involves using EEG and MRI as inputs, as shown in Figure 4. The segmentation process typically utilizes T1-weighted images with fat suppression for optimal imaging. It is crucial to consider structural abnormalities such as skull defects and lesions during segmentation to ensure the accuracy and effectiveness of the model. Open-source software, such as ITK-SNAP (Yushkevich et al., 2006), can be used for this purpose, though it can be time-consuming.

From Figure 4, a voxelated computational electromagnetic model is constructed using the segmentation results, where tissue types are assigned distinct voxels (small cubic cells). If MRI data is unavailable, standard head segmentation and electrode positions can be used as approximations. However, true personalization can only be achieved with patient-specific MRI data. Referring to Figure 4, with known electrode positions, likely source locations within the brain can be identified, typically within an evenly spaced region confined by the skull. Finally, a solution method for the forward model is selected. According to Beumer et al. (2022), three commonly used solution methods are available, each with its own advantages and disadvantages, as summarized in the published works.

The concept of combining EEG and MRI in the procedure outlined above is based on two key research findings. The first, by Faria et al., introduced the idea of using EEG electrodes for both stimulation and recording simultaneously (Paula-Faria, Fregni, Sebastião, Dias, & Leal, 2012). This combined EEG-tDCS application enabled the quantification of interictal events, providing a continuous recording of epileptiform activity during stimulation. This approach allows for real-time monitoring of efficacy and safety, as well as adjustments to electrode localization when necessary.

The second important study, conducted by (Tektürk et al.,2016), applied conventional tDCS on 12 patients with temporal lobe epilepsy. By combining EEG findings with cranial MRI, they were able to pinpoint the seizure focus more precisely. Other research efforts to develop personalized models have included the use

of 3D voltage maps (Varga et al., 2011) and MRI-based human head models (Cancelli et al., 2015), further advancing the potential for individualized treatment in epilepsy management.

### *2.7. Repetitive tDCS sessions*

The importance of the gap between successive tDCS sessions in inducing after-effects was highlighted in an animal study involving a genetically absent rat model (Assenza et al., 2014; Zoghi et al., 2016). While specific values for the optimal interval have not yet been firmly established, it was found that multiple tDCS sessions can prolong the after-effects, and the timing between sessions is crucial. Nitsche et al. (2008) suggested that the duration of the initial stimulation session impacts the ideal gap between sessions. For instance, when using a 4-second tDCS application, a 10-second interval is sufficient between sessions. However, if the effects are short-lived (around 10 minutes), a one-hour break is recommended; if the effects last longer (an hour or more), the gap should extend to between 48 and 72 hours. Conversely, for prolonged and stabilized effects, daily stimulation might be necessary.

Interestingly, studies have shown that homeostatic plasticity can influence the results of repeated stimulation. In the case of the human motor cortex, a second 5-minute stimulation session following a 3- to 10-minute rest can reduce or even reverse the inhibitory effects of the first stimulation, as observed by Fricke et al. (2011). However, after-effects were evidently prolonged and persisted for up to 30 minutes instead of 5 minutes when the interstimulus interval was less than 3 minutes. Zoghi et al. (2016) applied the 9-20-9 protocol, which consists of two 9-minute stimulations separated by a 20-minute rest, to a patient with drug-resistant temporal lobe epilepsy. Extended side effects were also reported here, including a notable reduction in seizure frequency that persisted for up to four months.

Monte-Silva et al. (2010) first investigated the ideal inter-stimulus interval for ctDCS in the motor cortex of 12 healthy adults. They created five treatment protocols, one of which was used by (Zoghi et al,2016). Following a single 9-minute session, the 9-0-9 procedure extended the aftereffects from 60 minutes to 40 minutes. The second session is administered during the first stimulation's aftereffects in both the 9-3-9 and 9-20-9 protocols. Although this may have the previously mentioned antagonistic homeostatic plasticity effects, in this study it resulted in an extension of the aftereffects from 60 to 120 minutes. Excitation-reduction was first diminished or eliminated, then re-established when the second session was given following the first session's aftereffects, i.e., in the 9-3h-9 and the 9-24h-9 protocols. According to the study's conclusion, delivering the second stimulation session while the aftereffects of the first session are still ongoing is the best way to extend and intensify their effects.

There were no studies that looked into the possibilities of changing the number of stimulation sessions to increase the effectiveness of ctDCS. (Yook Park, Seo, Kim, & Ko, 2011) used a current of 2 mA to provide 10 sessions of 20 minutes spaced at least one day apart to a patient with drug-resistant epilepsy. For at least two months, they demonstrated a notable reduction in the incidence and duration of seizures. Paula-Faria, Fregni et al. (2012) showed a substantial reduction in epileptiform activity only during tDCS after delivering three 10-minute sessions on a single day using EEG electrodes, although the exact intersession interval was not specified. However, neither of these experiments was sham-controlled.

On the other hand, patients with refractory focal epilepsy were gathered by (Yang et al. 2022) to participate in an extended phase of a prior three-arm, double-blind, multicenter, randomized sham-controlled, parallel trial on tDCS (Figure 5). Two groups of patients were assigned: one for active targeted tDCS (20 minutes per day) and another for enhanced tDCS (2 * 20 minutes per day). The patients receive repeated tDCS procedures every two to six months with each treatment phase lasting two weeks. The cathode, with a current intensity of 2 mA, was positioned above the epileptogenic focus.

Of the 19 participants in the extended phase, the active tDCS group included 11 patients who received between 2 and 16 sessions, while the enhanced tDCS group consisted of eight patients who received 3 to 11 sessions. From the first to the seventh follow-up, there was a considerable decrease in seizures, with a median reduction in seizure frequency ranging from 41.7% to 83.3%. Each enhanced tDCS session resulted in a significant 0.368-fold reduction in seizure frequency when compared to the standard protocol. However, across three treatment sessions and follow-ups, one patient showed an increase in total seizures by 8.5% to 232.8%.

Thus, the study provided new evidence suggesting that repeated ctDCS treatments over time may lead to sustained efficacy rather than treatment resistance.

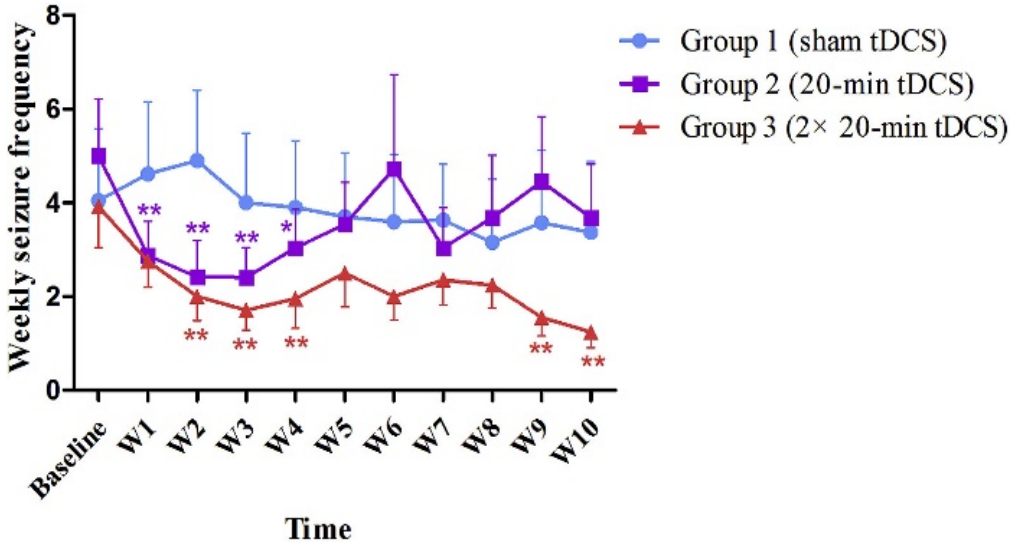


Figure 5. GEE(Generalized estimating equations) model estimated the mean weekly seizure frequency of three groups(Yang et al. 2022)

This study also showed an intriguing distinction between the effects of an increased stimulation treatment (2 * 20 minutes of tDCS daily) and a conventional procedure (20 minutes of tDCS daily).

### *2.8. Software Implementations*

Computational modeling of electrical fields within the brain is gaining increasing attention due to the relationship between local field intensity and treatment outcomes in neurostimulation. By predicting the effects of stimulation, researchers can better understand and control the variability in tDCS outcomes. This can help reduce the heterogeneity observed in tDCS treatment results. To perform neurostimulation calculations for personalized cHD-tDCS and tDCS, the use of electromagnetic simulation modeling software is essential. Examples of such software include Sim4Life, a commercial option ("SIM4LIFE » Zurich Med Tech," n.d.), and open-source tools such as SIMNIBS (Thielscher, Antunes, & Saturnino, 2015) and ROAST (Huang, Datta, Bikson, & Parra, 2019), which are specifically designed for neurostimulation purposes.

These tools facilitate more accurate modeling and personalization of neurostimulation therapies by optimizing electrode montages based on selected stimulation targets using source localization methods. The software programs can calculate the ideal placement of electrodes and the corresponding current doses for each patient, taking into account the patient's unique head topology. This ensures that the maximum field

strength remains consistent across different patients (Evans et al., 2020). By using such approaches, comparisons between HD-tDCS and tDCS studies can be conducted more effectively, allowing for better standardization of stimulation parameters and a clearer understanding of their impact on treatment outcomes.

### *2.9. Safety and Limitations*

Generally, the majority of clinical trials and research articles demonstrated the safety and efficacy of ctDCS or HD-tDCS techniques in gaining positive results for patients with DRFE such as decrease in IEDs frequency or seizure frequency. In fact, heterogeneity among different epilepsy subtypes across studies show the effectiveness of ctDCS or HD-tDCS as a treatment procedure for various forms of refractory focal epilepsy (Chacón & Gómez-Fernández, 2023).

It is important to note that the most common documented side effects caused by tDCS include tingling, local pain, itching or skin irritation on the stimulated region, along with drowsiness, fatigue and headache (Zewdie et al., 2020). However, some patients with DRE experienced an increase in seizure frequency for some unknown reasons.

Most studies and clinical trials investigating ctDCS and HD-tDCS for patients with DRE are characterized by small sample sizes. Additionally, there is a lack of direct comparisons between the effects of ctDCS and HD-tDCS, making it challenging to fully understand the relative efficacy of these two approaches. Furthermore, the majority of existing research fails to include long-term follow-up assessments, typically lacking evaluations extending two to three years.

There is a need for more multicenter clinical studies to further investigate the effects of ctDCS and HD-tDCS in combination with antiseizure medications (ASMs). Additionally, further research should explore the impact of repeated stimulation sessions and incorporate novel methods based on computational modeling to develop personalized stimulation protocols tailored to individual patient needs.

## 3. CONCLUSION

The use of HD-tDCS represents a promising advancement in the management of drug-resistant epilepsy (DRE). By delivering highly focal stimulation, cHD-tDCS enables targeted modulation of cortical excitability, allowing clinicians to inhibit neuronal firing specifically within epileptogenic regions. This increased spatial precision—achieved through smaller electrodes and optimized current distribution—offers a meaningful therapeutic alternative for patients who do not respond to conventional treatments.

Across clinical trials and case studies, cHD-tDCS has demonstrated encouraging outcomes, including reductions in intermittent epileptiform discharges (IEDs), seizure frequency (SF), and modifications in functional plasticity. These findings collectively support the safety and efficacy of HD-tDCS as a non-invasive and customizable neuromodulation technique for drug-resistant focal epilepsy. As such, HD-tDCS may become an important addition to existing treatment strategies for DRE.

Moreover, integrating HD-tDCS with advanced neuroimaging modalities—such as functional magnetic resonance imaging (fMRI) and transcranial magnetic stimulation combined with electroencephalography (TMS-EEG)—enhances its potential for precise targeting of epileptogenic networks. Coupled with real-time EEG monitoring, these approaches contribute to a more comprehensive understanding of how focal neuromodulation may influence seizure dynamics.

In conclusion, the growing body of research on HD-tDCS underscores the promise of personalized, focal, and non-invasive neuromodulation for improving seizure control and quality of life in individuals with drug-resistant epilepsy. Continued investigation through larger, rigorously designed clinical trials is essential to refine stimulation protocols, optimize electrode configurations, and further elucidate the complex neurological mechanisms underlying treatment response in DRE.

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