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با توجه به محدودیت‌های نرم افزاری، نتایج ارائه شده در این بخش نیازمند بررسی دقیق تر توسط کارشناس می‌باشد

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JIF ValueTrend of ImpactFactorTrend of ImpactFactor

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Year	JIF Value
۲۰۱۸	۲,۱۷۸
۲۰۱۹	۲,۲۰۸
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SJR ValueTrend of SJRTrend of SJR

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Year	SJR Value
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Cathodal HD-tDCS and attention: A study on patients with intractable left lateral frontal lobe epilepsy

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Cathodal HD-tDCS and attention: A study on patients with intractable left lateral frontal lobe epilepsy

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Abstract

Objective: Defects in the attentional network in patients with epilepsy are influenced by factors such as the location of epileptic foci. Examining the impact of cathodal high-definition transcranial direct current stimulation (HD-tDCS) on attention components could provide insights into potential attention-related side effects of tDCS. This study aimed to investigate the effect of cathodal HD-tDCS on interictal epileptiform discharges (IEDs), auditory/visual (A/V) attention components, and reaction time (RT) in patients with intractable focal left lateral frontal lobe epilepsy (LFLE).

Methods: To control for variations in individual epilepsy syndrome, 12 adult participants diagnosed with drug-resistant left LFLE with focal cortical IEDs on C3 underwent repeated measurements at pretest, posttest, and follow-up steps. 4×1 ring electrodes (cathode on C3 and four anodes on F3, P3, T3, and Cz) delivered 2 mA DC for 20 minutes per session for 10 consecutive days. The integrated visual and auditory continuous performance test (IVA+) assessed the A/V attention components and RT. One-way repeated-measure ANOVA was used.

Results: The findings suggest a significant effect in reducing IEDs. The IVA+ results showed a significant improvement in auditory divided attention and visual selective and focused attention ($p<0.05$). In the follow-up, these changes demonstrated lasting efficacy. A/V speed scales increased ($p<0.05$), showing a significant decrease in reaction time.

Conclusions: Cathodal HD-tDCS significantly reduced IEDs and improved the components of auditory divided attention, visual focused attention, and visual selective attention, with a reduction in patient reaction time. A significant lasting, side-effect-free positive effect was observed for up to one month after the intervention.

***Keywords*: **tDCS, focal seizures, attention component, lateral frontal lobe epilepsy, auditory/visual attention, reaction time

1. Introduction

Attention, a fundamental cognitive process, encompasses activities such as alerting and orienting to specific incoming stimuli and selecting pertinent information. These critical elements of attention play a pivotal role within executive control networks (Petersen and Posner, 2012). Epileptic conditions can significantly impact this network, leading to attention deficit syndromes (Englot et al., 2020; Zhang et al., 2009), and other cognitive impairments (Berg et al., 2008; Helmstaedter et al., 2020). The extent and nature of these deficits can vary based on several variables, including the location of epileptic foci, seizure frequency, seizure types, age of onset, duration of the disorder, antiepileptic drug use, and sociopsychological conditions (Quon et al., 2020; Ziaei et al., 2023). In adults with frontal lobe epilepsy, chronic attention and psychomotor speed impairments can lead to deficits in learning and intellectual abilities. Additionally, ADHD syndromes and a decline in executive functions are common in these patients (Berl et al., 2015; Cainelli et al., 2021; Patrikelis et al., 2016).

In recent years, there has been a notable increase in noninvasive transcranial direct current stimulation (tDCS)-based studies aimed at controlling epileptic seizures (Karvigh et al., 2017; Nitsche and Paulus, 2009; Yang et al., 2022) and improving cognitive functions such as attention and its components (Bandeira et al., 2016; Coffman et al., 2012; Gladwin et al., 2012), executive functions (Dockery et al., 2009), working memory (Cerreta et al., 2020; Ke et al., 2019), and motor learning (Guimarães et al., 2023). In addition, high-definition tDCS (HD-tDCS) applied to the dorsal anterior cingulate cortex improved cognitive flexibility and decision-making, indicating its potential use as a cognitive enhancer (Mattavelli et al., 2022). The application of HD-tDCS with a configuration of small electrodes has gained popularity for achieving more precise and targeted stimulation. The polarity (anode or cathode) and the extent of cortical modulation are determined by the central electrode of HD-tDCS, surrounded by three or more other electrodes (Villamar et al., 2013b). Anodal stimulation usually increases cortical excitability, whereas cathodal stimulation has an inhibitory effect in both tDCS and HD-tDCS (Nitsche & Paulus, 2000; Kuo et al., 2013). Initial findings indicate that conventional cathodal tDCS might result in improved management of seizures, especially in focal epilepsy, and it is generally considered safe, with no direct link to the occurrence of seizures in both adults and children diagnosed with drug-resistant epilepsy(Sudbrack-Oliveira et al., 2021). Some studies suggest that HD-tDCS is more effective than conventional tDCS (Breitling et al., 2020; Kuo et al., 2013). In this regard, the impact of HD-tDCS on attentional components is more pronounced than that of tDCS (Luna et al., 2020). Targeting the seizure-onset zone with HD-tDCS emerges as a prospective therapeutic approach for patients grappling with intractable focal epilepsy and shows the potential to diminish IEDs (Auvichayapat et al., 2013; Gschwind and Seeck, 2016; Regner et al., 2018; Rezakhani et al., 2022). However, the extent to which attention components are influenced by this stimulation remains unclear.

As far as our knowledge extends, no prior study has investigated attention components within both auditory and visual (A/V) modules in individuals with focal left lateral frontal lobe epilepsy (LFLE) undergoing cathodal HD-tDCS intervention, especially in refractory epilepsy cases. This investigation aims to provide a more comprehensive analysis by examining the hypothesis that cathodal HD-tDCS, when employed to regulate focal cortical interictal epileptiform discharges (IEDs), will improve auditory and visual attention components of attentional tasks as well as reaction time (RT) in individuals with drug-resistant left lateral frontal lobe epilepsy (LFLE) presenting focal cortical seizures.

2. Methods

2.1. Participants and experimental design

The participants in this study were adult patients with refractory focal cortical left LFLE who met the following inclusion criteria: (1) patients with no history of brain surgery and who were not candidates for surgery due to the ongoing complexity of their presurgical evaluation, (2) patients who were capable of comprehending and completing the Continuous Performance Test (CPT) with a minimum score of 50 in the normal range, (3) nonpregnant female patients, and (4) To maintain consistency in stimulation location, patients diagnosed with the left primary motor cortex as the seizure onset zone and the C3 region (10-20 system) as the epileptogenic area were selected in long-term video EEG monitoring (LTM). A total of 22 patients aged 22-31 years met the criteria, 12 of whom voluntarily participated and were enrolled in the study.

This research was approved by the Ethics Committee of Ferdowsi University of Mashhad (FUM). Before participation, patients were informed about the side effects of tDCS and the protocol procedure, and both patients and their parents gave written informed consent. Patients were duly informed that HD-tDCS could result in either improvement or worsening of their seizures, with the understanding that the effects would be temporary. They also gave their consent to the publication of the research results.

A repeated-measures design was employed with pretest, posttest, and follow-up (conducted after 1 month) to control for individual differences in epilepsy syndromes. Three participants were unable to complete the integrated visual and auditory continuous performance test (IVA+) pretest because of the severity of their cognitive impairment. They were excluded from the research at the beginning, and two of them left the experiment. Therefore, data analysis was performed on 7 participants, whose demographic and primary epilepsy data are presented below.

Table 1. Patient demographic and primary epilepsy data (n = 7)

	Cathodal HD-tDCS
No. of subject	7
Sex (male/female)	4/3
Age	
Mean ±SD	24.85±2.96
Range (years)	22-31
Diagnosis	
Focal seizures without secondary generalization	5
Focal seizures with secondary generalization	2
Etiologies of epilepsy	Focal cortical
Epileptogenic region	C3
Seizure onset zone	Left primary motor cortex
MRI finding	Negative
Age at the onset of seizures (years)	9.7±2.6

The number of antiepileptic drugs used:	
No. of subject	**Antiepileptic drugs**
3	1) ZNS, CLZ 2) ZNS, CBZ

	3) CBZ, LEV
3	1) CBZ, LEV, Valproate 2) CBZ, LMT, Valproate 3) OCBZ, CLB, PHT
1	1) PHB, PRM, CBZ, ZNS, Valproate

CBZ: carbamazepine; CLB: clobazam; CLZ: clonazepam; LMT: lamotrigine; LEV: levetiractam; PHB: phenobarbital; PHT: phenytoin; PRM: primidone; OCBZ: oxcarbazepine; ZNS: zonisamide.

a. IEDs counting

EEG recording was utilized, following an 18-channel 10-20 system double banana longitudinal bipolar montage configuration. Baseline EEG recordings were conducted over one hour of controlled wakefulness to record the IEDs (Karvigh et al., 2017; Rezakhani et al., 2022). Subsequently, EEG recordings were obtained immediately after the last stimulation session and once again one month after the final stimulation session. An epileptologist, blinded to the intervention and clinical observations, reviewed EEG recordings and manually tabulated occurrences of both focal and generalized IEDs.

2.2. Attention component assessment

The Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) based IVA+ test was administered to evaluate the A/V attention components and response control. The test duration was approximately 20 min, including a warm-up and cool-down session, and the main body of the test lasted for 13 min. The test comprised 500 A/V stimuli, with "1" and "2" representing the target and nontarget stimuli, respectively. The IVA+ test is initiated with the measurement of an individual's performance without any prior exposure or practice (warming-up step). This step is undertaken to establish a reference point, alleviate any anxiety, and improve task comprehension. Subsequently, the subject's results during the main test and cooling-down step are compared to their initial baseline performance to effectively control the practice effects. The standard scores of attention components were calculated by determining the arithmetic mean of the IVA+ attentional scales set for each attention component (Sandford and A. Turner,

2009) (Table 2). The IVA+ tests were conducted using the Brain Train Test Battery II (version 2008.1), which was installed on a laptop with a 15.6-inch HD (1366×768) LED LCD monitor. A uniform optical mouse was used by all participants to respond to the target stimuli. The tests were administered between 10 a.m. and 2 p.m.

Table 2. Attention components for both auditory and visual modules, scales, and definitions

Attention components	Attentional Scales	Definition
Focused attention	Prudence and Vigilance	The correct response to visual and auditory stimuli of the test (i.e., "1").
Alternative attention	Speed, Balance, Readiness, Consistency, and Focus	Cognitive Flexibility in Attention Transmission.
Sustain attention	Stamina, Focus, and Consistency	Maintaining a Responsive Pattern is sustainable and Valid.
Divided attention	Speed, Prudence	Ability to respond simultaneously to different tasks.
Selective attention	Prudence, Comprehension, and Vigilance	Cognitive ability to correct responses to target stimuli and inhibition response to nontargets.

2.3. Reaction time (RT)

The IVA+ test's speed scale assesses the RT when correctly responding to both A/V target stimuli ("1"), which is calculated using the mean A/V RT in milliseconds for all correct responses. This scale evaluates the speed of discriminatory cognitive processing.

2.4. HD-tDCS protocol

In this study, a battery-driven direct current stimulator (Activates ® II; Iontophoresis Delivery Unit, USA) was utilized, with 4×1 ring electrodes (11 mm outer radius and five mm inner radius) and a four-to-one wire adapter. Ag/AgCl electrodes were placed inside special plastic cylinders with a diameter and height of 12 mm and were filled with EEG conductive gel for optimal current flow. The cathodal electrode was placed on C3, the epileptogenic zone identified by long-term monitoring (LTM), while the four anodal electrodes were placed according to the international 10-20 system on F3, T3, P3, and Cz (Villamar et al., 2013a). This arrangement was secured using a modular EEG cap. Impedances were verified using an ampere meter device. A 4*0.5 mA DC anodal current was administered for 20 min with 15 s ramp-up and ramp-down periods (Fig. 1). The cathodal electrode site (C3) serves as a current sink, absorbing a total of 2 mA (4 * 0.5 mA). HD -tDCS was performed once daily for 10 consecutive days. A specialist monitored patients during the stimulation sessions and for one hour after the procedure to detect any immediate side effects (Brunoni et al., 2012). Electric field simulation of HD-tDCS was performed with simNIBS 4.0.1 software using standard MNI data (Thielscher et al., 2015).

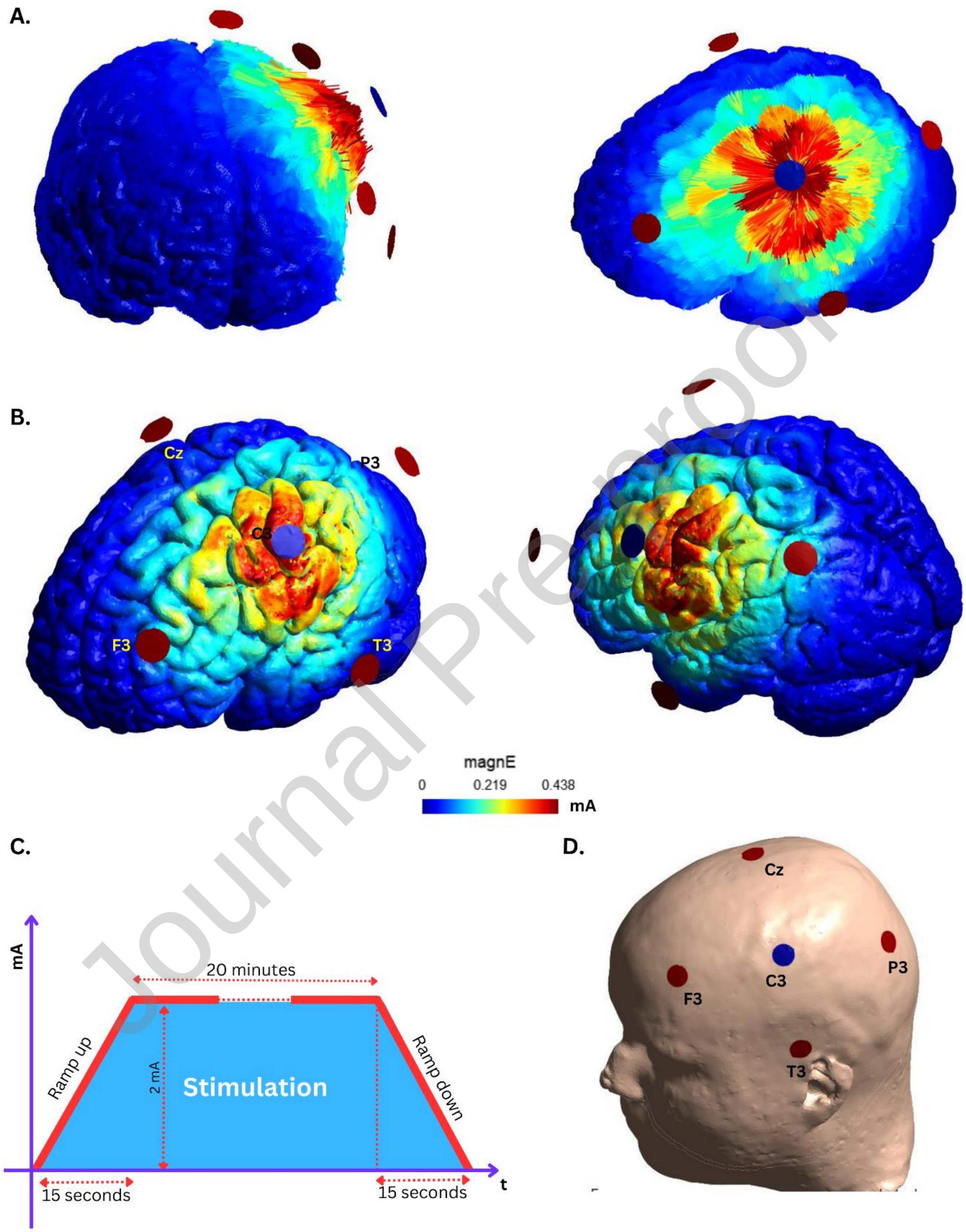

Fig. 1: A. Simulation of the electric field distribution up the cortex in cathodal HD-tDCS.; B. Current distribution on the cortex in simulation.; C. DC stimulation schematic diagram.; D. Electrode placement simulation on the scalp.

3. Data analysis

To control for individual differences in epilepsy syndrome, all procedures were administered to the same group of participants in three steps. One-way repeated-measures ANOVA with Bonferroni correction was employed to assess the differences in measurements. Greenhouse-Geisser was used to address violations of the sphericity assumption in repeated-measures ANOVA. The statistical analysis was performed with a significance level of $\alpha = 0.05$ and a confidence interval of 95%. The p-value was considered significant if it was less than or equal to 0.05.

4. Results

All patients completed ten HD-tDCS sessions without any complications. Mild skin redness and itching in the stimulated area were observed; however, no significant adverse effects were reported during or after the stimulation sessions until the one-month follow-up.

4.1. IEDs

The IED data analysis revealed a violation of the assumption of sphericity ($p < 0.05$). To address this, the corrected test for within-subjects effects was conducted using the Greenhouse-Geisser correction ($F(1.115, 6.69) = 6.668$, $p = 0.036$). These results indicate a significant effect within the examined measures (Fig.2).

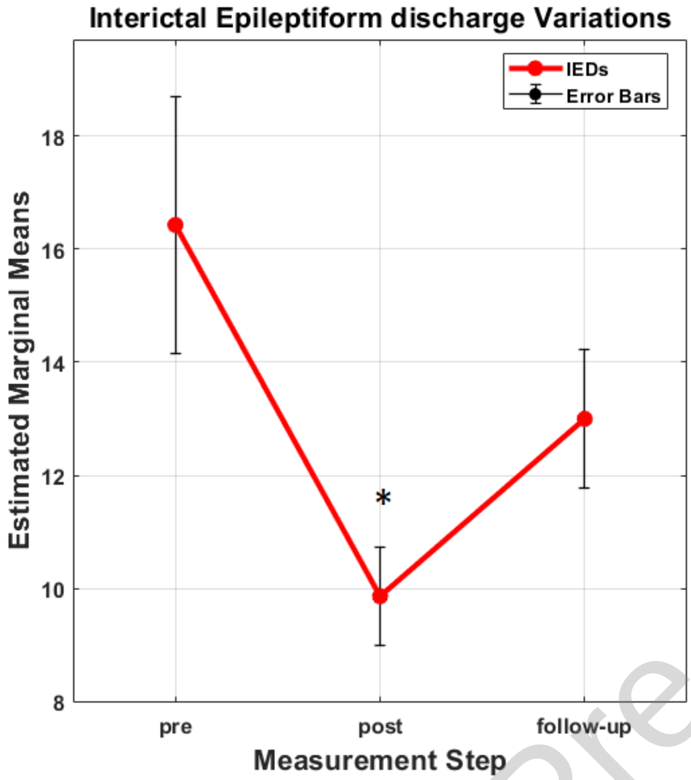

Fig. 2. Estimated marginal means of IEDs at three steps of the study; *****: statistically significant difference ($p < 0.05$).

4.2. A/V- Attention Components

The statistical analysis results for the five A/V components, namely selective, focused, divided, alternative, and sustained attention, are presented in Table 3.

Table 3. The results of repeated-measure ANOVA

Module	**Attention Components**	**Mauchly's Test of Sphericity**		**Tests of Within-Subject Effects**			
		χ^2	*P*	*IV df, error df*	*F*	*P*	$\eta p2$ η_p^2
Auditory	Selective	2.02	0.364	2, 12	3.83	0.052	0.39
	Focused	3.94	0.139	2, 12	2.38	0.134	0.28
	Divided	2.58	0.275	2, 12	5.79	0.017 *****	0.49
	Alternative	0.34	0.840	2, 12	0.79	0.47	0.11
	Sustained	3.56	0.169	2, 12	0.15	0.86	0.02
Visual	Selective	0.47	0.791	2, 12	4.30	0.039 *****	0.42

	Focused	1.33	0.513	2, 12	5.82	0.017 *	0.49
	Divided	6.37	0.041	1.16, 6.97 †	3.70	0.093	0.38
	Alternative	0.99	0.609	2, 12	0.41	0.671	0.06
	Sustained	1.20	0.547	2, 12	0.37	0.698	0.06

†: For the data that violated the assumption of sphericity, we report a Greenhouse-Geisser correction;
*: significantly different ($p < 0.05$).

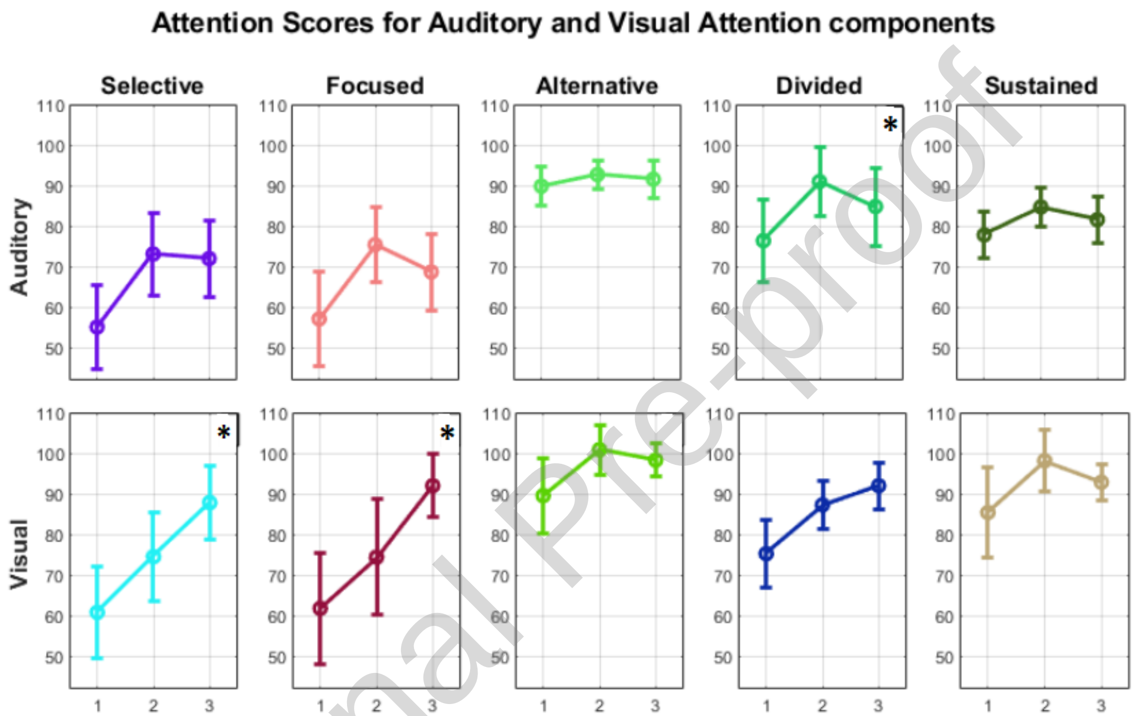

Fig 3. Mean variations of standard scores for auditory and visual attention components in three steps of the study, x-axes: 1: pretest, 2: posttest, 3: follow-up; y-axes: mean of standard score *: significantly different ($p < 0.05$).

4.3. The speed scale of the IVA+ test

Figure 4. presents the mean variations of standard scores in the A/V Speed scales related to the three steps of the IVA+ test. After the intervention, the speed scores in the A/V modules increased significantly, but in the follow-up measurement, they returned to the initial level. These differences were statistically

significant for auditory speed ($F (2, 12) = 4.39$, $p=0.037$, $\eta_p^2=0.42$) and visual speed ($F (2, 12) = 4.84$, $p=0.029$, $\eta_p^2=0.45$).

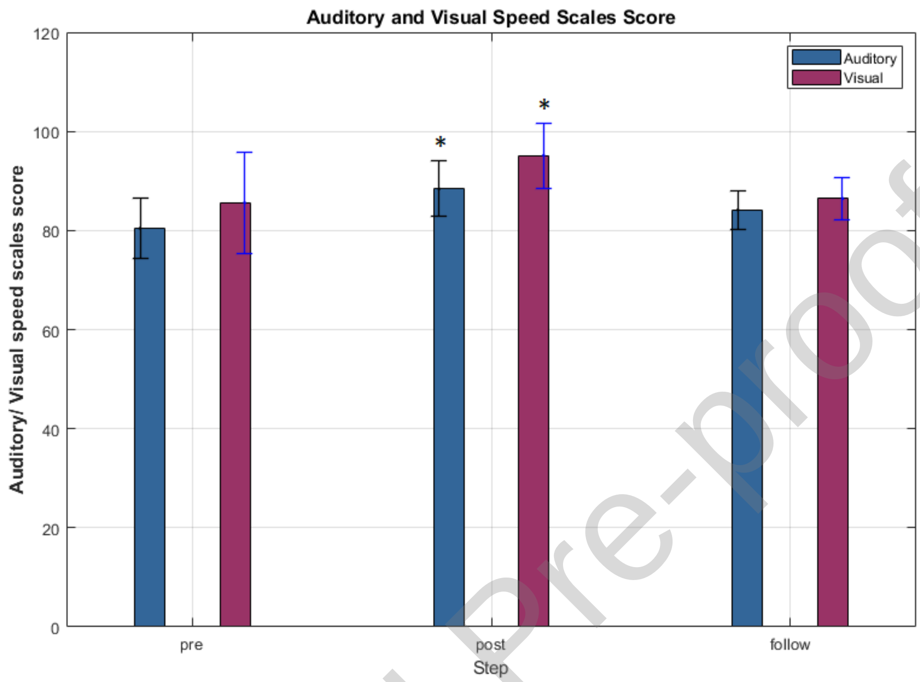

Fig. 4. The mean variations of standardized scores in auditory/visual speed scales at three steps of the study; *****: significantly different ($p < 0.05$).

5. Discussion

tDCS manipulates excitability by modulating neuronal membrane subthreshold and initiates long-term potentiation or depression, which are pivotal in the foundational processes of diverse cognitive functions and are associated with pathological changes seen in various brain disorders (Stagg et al., 2018). Sudbrack-Oliveira and colleagues (2021) demonstrate cathodal HD-tDCS as a promising noninvasive therapy for drug-resistant focal epilepsy. A two-week stimulation protocol yielded significant reductions in IEDs and seizure frequency compared to the sham group (Sudbrack-Oliveira et al., 2021).

The findings of this investigation provide further validation of the potential effects of cathodal HD-tDCS in addressing the challenges faced by individuals dealing with refractory left lateral frontal epilepsy. Notably, the promising lasting effect was evident when assessing the outcomes one month after intervention. These findings align with the results of controlled investigations carried out on patients with intractable epilepsy (Fregni et al., 2006; Yang et al., 2020). Diminishing neuronal excitability stands as a shared objective within antiepileptic treatments. Cathodal tDCS results in cortical inhibition, a crucial aspect relevant to the management of epilepsy (Nitsche and Paulus, 2009).

A central objective of our study was to investigate the impact of cathodal HD-tDCS on A/V attention components, as assessed using the IVA+ test. The results showed a significant improvement in auditory divided attention, visual selective attention and visual focused attention after the intervention, which was sustained in the follow-up step. However, improvement in auditory divided attention was not observed until the follow-up step.

To better understand this improvement, some essential points need to be considered. First, the 4×1 arrangement of HD electrodes forms a rhombus with the corners of P3, C3, T3, and Cz. The current flows from the anodal source in each corner to the cathode (current sink) in C3. Modeling of the current distribution in the brain cortex by Villamar et al. demonstrated that the polarity of 100% is cathodic at the center of cathodal HD-tDCS (Villamar et al., 2013b). However, this value is linearly reversed as we move toward the anode electrodes, and the polarity changes to 75% anodic. It is well known that anodal stimulation generally increases excitability (Nitsche and Paulus, 2000).

Second, the primary nodes of the frontoparietal network are adjacent to anode electrodes; P3 is located on the left posterior parietal cortex (PPC), and F3 is ipsilaterally near the frontal eye field (FEF). These are critical areas of selective attention control with connections to subcortical regions (Knudsen, 2018). In addition, left PPC subregions, including the IPS and LIP, play an essential role in attention control

(Bourgeois et al., 2020). The efficacy of tDCS on the PPC (Moos et al., 2012) and dorsolateral prefrontal cortex (DLPFC) regions in the left hemisphere is in line with improved attentional selection function (Gladwin et al., 2012, Lefaucheur et al., 2017).

Research has revealed the brain as a large-scale dynamic network. Excitatory stimulation in one area can surprisingly reduce excitability in connected regions. Polanía and colleagues (2012) showed that anodal tDCS applied to the primary motor cortex reduced excitability in the contralateral motor cortex. This finding implies that tDCS-induced neuroplastic changes may be associated with alterations in functional connectivity (Polanía et al., 2012). Kunze and colleagues (2016) indicated that the interaction between network areas led to the emergence of new dynamic states compared to isolated regions. These results suggest that synchronization plays a crucial role in the alterations of spatiotemporal patterns induced by tDCS (Kunze et al., 2016).

Our findings demonstrate a noteworthy improvement in auditory divided attention. These results are consistent with an fMRI study that highlights the importance of the superior temporal gyrus (STG), which is located adjacent to the T3 electrode, as well as the parietal cortex regions, in tasks requiring selective audiovisual attention. Additionally, this study demonstrated that the aforementioned regions, along with the frontal eye field (FEF), are also critical in divided audio-visual attention (Moisala et al., 2015). The left prefrontal cortex (PFC) plays an integrative role in many cognitive functions, including the ability to flexibly control top-down attention. Therefore, stimulation of the left dorsolateral prefrontal cortex (DLPFC) can significantly impact the attentional system (Clarke et al., 2020; Yadollahpour et al., 2017).

The speed scale in the IVA+ test measures the mean response time (RT) of all correct responses to target stimuli. An increase in the speed score indicates a decrease in RT and vice versa (Arble et al., 2014; Prinzmetal et al., 2005). The significant increase in the audio-visual speed score (Fig. 3) reflects a reduction in RT and predicts improvement in attentional performance. This improvement was observed in all attention components, including divided, focused, and selective attention. According to the current distribution and affected areas, tDCS modulates the processing units (minicolumns) in the cortex, thereby affecting processing speed and learning mechanisms (Lücke and Von der Malsburg, 2004). Experimental evidence confirms that both cathodal/anodal tDCS and HD-tDCS can reduce RT in various functional areas in both healthy individuals and patients (Filmer et al., 2013; Lücke and Von der Malsburg, 2004).

The effects observed in attention components following cathodal HD-tDCS may be influenced by the decrease in IEDs. Previous research has indicated that IEDs have been linked to diminished cognitive function(Liu et al., 2016). Research has shown that suppressing IEDs with antiepileptic therapies can lead to improved cognitive performance (García-Peñas, 2011; Warsi et al., 2023). Moreover, investigations have identified a slight adverse impact of the IED index on cognitive aspects, including P300 and mismatch negativity (MMN) (Sun et al., 2019). These collective results imply that alterations in IEDs play a vital role in both the pathophysiology of epilepsy and the mechanisms contributing to cognitive disorders (Novak et al., 2022). However, further research is needed to elucidate the precise nature and extent of the link between IED reduction and attention components in the context of cathodal HD-tDCS interventions.

Changes in intrinsic brain connectivity networks demonstrated a robust association with the transient effects of IEDs (Shamshiri et al., 2017). IEDs establish significant alterations in dorsal attention networks (Ibrahim et al., 2014) including visual motion area, frontal eye fields, superior parietal lobule, intraparietal sulcus, and ventral premotor cortex. The therapeutic impact of Cathodal HD-tDCS on IDEs may also affect this network.

While tDCS presents the potential for modulating neural activity (Nitsche and Paulus, 2000) and cognitive processes (Cerreta et al., 2020; Coffman et al., 2012; Dockery et al., 2009; Ke et al., 2019), the complex interplay of attentional networks and individual variability contributes to outcome variations (Chechlacz et al., 2015). Nevertheless, the inconsistent significance observed in certain attentional components underscores the complex nature of attention (Styles, 2005) and the challenges in precisely modulating it with tDCS. Variables such as the specific attention task (Towey et al., 2019), stimulation duration and intensity (Villamar et al., 2013a), and electrode site selection (Martin et al., 2023) may interact in ways leading to nonsignificant findings. This divergence between predicted outcomes and empirical results underscores the necessity for further research to refine tDCS protocols, gain deeper insight into attention nuances, and untangle the complex relationships between brain regions engaged in attentional processes. Spatial resolution limitations may be encountered in EEG recordings typically conducted to identify IEDs in cases of focal cortical epilepsy. As a future direction, the need for advanced and cost-effective methods to detect the sources of IEDs should be considered. Besides, the group size is a notable restriction of this research. We acknowledge the necessity for future investigations involving a more statistically robust population with a sham intervention group. Such endeavors will undoubtedly enrich our understanding of the intricate impact of attentional components on these individuals.

6. Conclusion

The study findings indicate that the use of cathodal 4×1 HD-tDCS on C3 with array anodes on F3, P3, T3, and Cz significantly diminished IEDs and improved the performance of auditory divided attention and visual focused and selective attention components in patients with drug-resistant LFLE with focal cortical seizures. The results also showed a decrease in RT, and the lasting effects were promising a month after the intervention. Moreover, the intervention did not have any adverse side effects and was well tolerated by the patients. Based on these findings, the prospective utilization of cathodal 4x1 HD-tDCS as an intervention for the mitigation of focal left lateral frontal epilepsy holds promise. Furthermore, the assessment of its effects on the attention component has indicated utility and safety. Nevertheless, further refinement of controlled experimental designs is necessary to increase the robustness of the observed effects.

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Declarations of competing interest

None.

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Highlights:

- Cathodal HD-tDCS significantly reduced interictal epileptiform discharges (IEDs).
- Auditory divided attention and visual selective/focused attention improved in the IVA+ assessment.
- Reaction time substantially improved, implying improved auditory/visual processing speed.
- Results confirmed a lasting and tolerated positive effect of cathodal HD-tDCS for up to one month on some attention components.