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Stereo-EEG based personalized multichannel transcranial direct current stimulation in drug-resistant epilepsy

Maëva Daoud¹, Ricardo Salvador³, Nada El Youssef², Alexane Fierain², Elodie Garnier¹, Maria Chiara Biagi³, Samuel Medina Villalon^{1,2}, Fabrice Wendling⁴, Christian Benar¹, Giulio Ruffini³, Fabrice Bartolomei^{1,2,*}

¹ Aix Marseille Univ, CNRS, CRMBM, Marseille, France

² APHM, Timone Hospital, Epileptology and Cerebral Rhythmology, Marseille, France

³ Neuroelectrics Barcelona, Av. Tibidabo 47 bis, 08035 Barcelona, Spain

⁴ Univ Rennes, INSERM, LTSI-U1099, F-35000, Rennes, France

*** Corresponding author:**

Prof. Fabrice Bartolomei, MD, PhD

Service d'Epileptologie et de Rythmologie cérébrale, Hôpital Timone, 264 Rue Saint-Pierre, 13005, Marseille, France

Tel.: +33491385833

Fax: +33491385826

E-mail: fabrice.bartolomei@ap-hm.fr

Highlights

- We used personalized multichannel tDCS to target the epileptogenic zone identified by stereoelectroencephalography (SEEG).
- After 6 months with 3 cycles of 5 consecutive days of tDCS treatment (2 x 20 min per day), half of the patients were responders.
- The efficacy of tDCS in responders was associated to a significant decrease in functional connectivity measured from scalp EEG.

Abstract

Objective: In epilepsy, multichannel transcranial direct electrical stimulation (tDCS) is applied to decrease cortical activity through the delivery of weak currents using several scalp electrodes. We investigated the long-term effects of personalized, multisession, stereotactic-EEG (SEEG)-targeted multichannel tDCS on seizure frequency (SF) and functional connectivity (Fc) as measured by EEG in patients with drug-resistant epilepsy (DRE).

Methods: Ten patients suffering from DRE were recruited. Multichannel tDCS (Starstim, Neuroelectronics) was applied during three cycles (one cycle every two months) of stimulation. Each cycle consisted of five consecutive days where patients received tDCS daily in two 20 min sessions separated by 20 minutes. The montages were personalized to target epileptogenic area of each patient as defined by SEEG recordings. SF during and after treatment was compared with baseline. Fc changes were analysed using scalp EEG recordings.

Results: After the last tDCS session, five patients experienced a SF decrease of 50% or more compared with baseline (R: responders, average SF decrease of 74%). We estimated Fc changes between cycles and across R and non-responder (NR) patients. R presented a significant decrease in Fc ($p < 0.05$) at the third session in alpha and beta frequency bands compared to the first one.

Conclusions: Multichannel tDCS guided by SEEG is a promising therapeutic approach. Significant response was associated with a decrease of Fc after three stimulation cycles.

Significance: Such results suggest that tDCS-induced functional plasticity changes that may underlie the clinical response.

Keywords: Drug-resistant epilepsy, Multichannel transcranial direct current stimulation (tDCS), Patient-specific approach, functional connectivity, Electroencephalography.

Abbreviations:

tDCS: Transcranial Direct Current Stimulation. SEEG: Stereoelectroencephalography. EEG: Electroencephalography. DRE: Drug-resistant Epilepsy. SF: Seizure Frequency. Fc: Functional connectivity. R: Responder. NR: Non-responder. MRI: Magnetic Resonance Imaging. IQ: Intelligence Quotient. AEs: Adverse events. ICA: Independent Component Analysis. EMG: Electromyography. LMM: Linear Mixed Models. REML: Restricted Maximum Likelihood. LSM: Least Squares Means. SOZ: Seizure Onset Zone. VNS: Vagus Nerve Stimulation. SMA: Supplementary motor area. SZs: Seizures. FCD: Focal cortical dysplasia. SGTC: Seizure generalized tonico-clonic. ASM: antiseizure medication. M-2, M-1: 1 and 2 months before the first stimulation cycle; M1C1: one month after the first cycle; M2C1: two months after the first cycle; M1C2: one month after the second cycle; M2C2: two months after the second cycle; M1C3: one month after the third cycle; M2C3: two months after the third cycle. M1: first month. M2: second month. C1: Cycle 1. C2: Cycle 2. C3: Cycle 3. Strength D5-D1: Strength Day 5 – Strength Day 1 (after – before tDCS cycle).

1. Introduction

One-third of patients with epilepsy have seizures refractory to pharmacotherapy (Brodie and Kwan, 2002; Devinsky et al., 2018). The only curative treatment is surgery and in this context stereoelectroencephalography (SEEG) is increasingly used in presurgical assessment (Baud et al., 2018; Jehi et al., 2015). However, epilepsy surgery is only possible in a limited number of cases (15-20%) and is associated with a relatively high number of failures (Baud et al., 2018). Consequently, alternative treatments based on non-invasive brain stimulation methods aiming at decreasing cortical excitability represent a promising therapeutic. Transcranial direct current stimulation (tDCS) is an emerging non-invasive method of brain stimulation involving passing a weak current (1–2 mA) across the head tissue (scalp, skull, cortex) using scalp electrodes positioned on the head (San-juan et al., 2015). This neuromodulatory technique could modulate brain excitability by subthreshold membrane depolarization or hyperpolarization. As the electric field under the anode is predominantly excitatory, and the one under the cathode is predominantly inhibitory (Nitsche et al., 2003; Nitsche and Paulus, 2000), in epilepsy, the target region must be in the field of a cathode to achieve cerebral inhibition. tDCS effects depend on several factors including stimulation duration, current intensity, number of repetitions, duration of the interval between stimulation sessions, number, and localization of electrodes. Indeed, conventional tDCS montage employs only two large electrodes (one anode and one cathode) whereas multichannel tDCS, uses several smaller pairs of electrodes that potentially enhance and optimize stimulation focality (Villamar et al., 2013). Furthermore, the current values and electrode positions can be determined from computational head models and account for the geometry and conductive properties of the head tissues in order to accurately calculate the induced electric field, making it possible to target brain regions with more accuracy (Sadleir et al., 2012).

In this way, several human and animal studies have shown the efficacy of cathodal stimulation for decreasing the number of epileptiform discharges (Fregni et al., 2006; Lian et al., 2003; Yook et al., 2011). However, the majority of previous studies employed generic bipolar montages with large sponges applied during one or a few treatment sessions and without personalization. Recently, a study involving drug resistant epilepsy patients employed multielectrode montages that were designed using a realistic

head model-driven approach to drive an inhibitory electric field to the target cortical epileptic region (Kaye et al., 2021). This study used a generic head model and a definition of the epileptogenic zone based solely on non-invasive recordings. Since tDCS electric-fields are affected by individual brain anatomy, a patient-specific approach is more suited to properly engage the targeted brain region (Laakso et al., 2015; Miranda et al., 2013; Ruffini et al., 2014).

We report here a pilot study investigating the efficacy of an individualized multichannel tDCS protocol based on the patient's anatomy and epileptogenic network. We selected a population of patients with focal epilepsy considered as inoperable (or failing after surgery) and whose epileptogenic zone was clearly identified by prior SEEG recordings. This specific population was selected because the patients have severe epilepsy with no other therapeutic resources and they had SEEG procedure favoring optimal targeting for multichannel cathodal tDCS, especially for epilepsies with normal MRI or a complex epileptogenic zone exceeding lesion boundaries. Moreover, the neuromodulatory mechanisms associated with the application of a low-frequency electric field remain poorly understood. Drug-resistant focal epilepsies are associated with interictal alterations in Fc, characterized in particular by increased neural synchrony in most epileptogenic regions (Bartolomei et al., 2017; Bettus et al., 2008; Lagarde et al., 2018). Thus, we sought to correlate the clinical efficacy of our tDCS protocol with changes in functional connectivity (Fc) measured from scalp EEG recordings. We hypothesized that the efficacy of multichannel tDCS is associated with Fc-specific changes.

2. Methods

2.1 Patients

Ten patients with drug-resistant focal epilepsy were enrolled in this study (7 male, 3 female); mean age 29.9 years; range 12-60 years).

Inclusion criteria were the following: (1) ≥ 12 years of age; (2) diagnosed with focal drug-resistant epilepsy not operable or presenting a failure of previous epilepsy surgery with at least 3 seizures per month during the baseline (before the first session of tDCS treatment) for at least 3 months; (3) SEEG

previously performed before inclusion with an adequate definition of unifocal epileptogenic zone; (4) have stable medications for epilepsy for the whole study duration (5) Total IQ > 55; (6) be able to understand, speak and write in French.

Exclusion criteria were the following: (1) skin conditions (e.g., eczema, lesions) on the scalp; (2) any cranial metal implant; (3) or implanted devices (i.e. cardiac pacemaker, deep brain stimulator, cochlear implant, medication infusion pump); (4) previous surgeries opening the skull leaving skull defects with a radius \geq to 5mm; (5) persons protected by articles L1121-5, L1121-6 and L1121-8 of Public Health Code (pregnant or breastfeeding woman, deprived of liberty by judicial decision, situations of social fragility, adults unable to express their consent).

The general characteristics of the patients are summarized in Table 1. This study was approved by the local ethics committee. Written informed consent was obtained from each patient or his or her legal representative before inclusion in the study.

2.2 Experimental design

This is a prospective, open labelled, monocentric pilot study in patients with medically refractory epilepsy followed during 8 months with patients acting as their own internal control

For each patient, after a baseline period of at least two months, the study started with a 1-hour EEG exam (Electroencephalography) on day 1 of the week (before stimulation) in order to collect electrophysiological brain state right before stimulation treatment at the end of the baseline period. Then, each day of each stimulation cycle period (a cycle consisted of 5 consecutive days of stimulation), patients received tDCS treatment with a mean total injected current of 1.99 mA. The daily treatment was organized in two periods of 20 minutes of stimulation (a bi-session) each separated by 20 minutes off (i.e., with 40 minutes of cathodal stimulation in total). At the end of each cycle (on the 5th day), another EEG exam of 1 hour was performed for comparison with the one obtained before tDCS treatment at the first day of the cycle. Each cycle was repeated every two months, for a total of 3 times (six months in total)(see figure 1).

2.3 Personalized multichannel cathodal tDCS

The electrode montage was determined individually based on a montage optimization pipeline. Biophysical head models were created from structural images of each patient (T1-weighted MRIs), using the methods described in (Fischer et al., 2017). We used MRI acquisitions performed before the SEEG. These models included lesions such as previous corticectomies. Montage optimization was performed with the Stimweaver algorithm (Ruffini et al., 2014). In short, this method takes as input a target E-field map, defined on the personalized cortical surface of the head model created for each patient. This target map contained information about the areas to inhibit (identified by SEEG recording previously acquired Fig. 2) and of areas to leave unaffected by stimulation. The latter corresponded to silent areas, defined as the cortical areas with normal EEG activity or with the smallest amount of epileptogenic activity. The region to be inhibited (target) was defined according to the definition of the epileptogenic zone obtained from SEEG. It was based on visual analysis according to classical rules of interpretation (Bartolomei et al., 2008) and quantification using epileptogenicity index (EI). The EI combines analysis of both spectral and temporal features of SEEG signals, respectively, related to the propensity of a brain area to generate fast discharges (12.4–127 Hz), and to the earliness of involvement of this area in the seizure (see details in (Bartolomei et al., 2008)).

The algorithm then automatically identified the positions of electrodes and associated currents that resulted in the E-field distribution that better approximates the target. This solution was constrained to a maximum number of electrodes (8), maximum current per electrode (1.884 mA, in absolute value) and maximum total injected current (2.0 mA). The electrode positions were constrained to a subset of positions of the 10-10 EEG system. Typical montages involved cathodes over the areas to inhibit and anodes over the silent areas. Stimulation was applied via a multichannel tDCS system (Starstim8, Neuroelectronics Barcelona). The stimulation protocol was created and monitored using the NIC 2.0 software (www.neuroelectronics.com/products/software/nic2/). The electrodes (NG PiStim electrodes, 1 cm radius, cylindrical Ag/AgCl electrodes with a layer of conductive SIGMA gel underneath) were positioned in a neoprene cap with the 39 positions used in the montage optimization (Neuroelectric's Standard Cap). The current was gradually ramped-up over a period of 15 seconds until reaching an intensity up to 2.0 mA and delivered in two periods of 20 min separated by 20 min off. The break

between sessions of tDCS may be crucial for optimizing cumulative effects and for prolongating the inhibitory neuroplastic effects of cathodal stimulation (Monte-Silva et al., 2010). A recent study (Yang et al., 2020) has found a superior significant effect using a protocol of 2x20 min stimulation per day with a 20 min interval, compared with a protocol using 40 min stimulation only (without interval).

At the end of each period, the currents ramped-down for a period of 15 seconds. These parameters have previously been shown to be well tolerated in healthy subjects and in other clinical conditions (Borckardt et al., 2012; Yang et al., 2020).

2.4 Electroencephalogram recordings

EEG was performed using 21 channels EEG cap using a Natus apparatus (Natus, France, sampling rate 256 Hz). Signals were acquired during one hour with at least 10 min eyes-closed resting state, and at distance from seizures or post-ictal state (at least 3h). EEG recording was obtained before the start of stimulations (baseline), before each cycle of personalized multichannel tDCS and at the last day of each cycle, immediately following the last stimulation period. The electrodes were arranged based on the international 10–20 system.

2.5 Clinical outcome

The patients or their relatives were instructed to record the number and type of seizures in a calendar (seizure diary) two months before (the baseline) the beginning of the study until two months after the last stimulation-period of multichannel tDCS. The records were evaluated each month to count the number of seizures for each period (before, during, shortly after and a long-time period after each cycle of tDCS). Reduction and increase in the number of seizures were represented as a percentage compared to the baseline. Patients whose seizures were reduced by at least 50% in frequency after tDCS cycles were qualified as “responders”. Others were qualified as “non-responders”. Furthermore, patients were asked to notify any perceived adverse effect of tDCS, during and after each bi-session of 20-minutes stimulation. All adverse events (AEs) were recorded.

2.6 Data analysis and functional connectivity

EEG recordings were analysed using AnyWave software (Colombet et al., 2015). A post recording bandpass filter (notch) was applied to signals to remove 50 Hz noise (powerline frequency band in Europe), frequencies below 0.5 Hz and above 70 Hz. The sampling frequency was 256 Hz. We first removed artifacts using independent component analysis (ICA) (Barbati et al., 2004). Then, the EEG recording was inspected visually, and all segments containing artifacts not identified by the ICA analysis were rejected (cardiac, muscles, and eye movement artefacts were eliminated). Interictal spikes were automatically quantified in AnyWave using Delphos (Detector of ElectroPhysiological Oscillations and Spikes) (Roehri et al, 2016).

Then, we estimated the functional connectivity in the theta (4-8 Hz), alpha (8-13 Hz) and beta (13-30 Hz) frequency bands. We did not include gamma activity in this analysis because fast electrical rhythms recorded in the scalp (30-100 Hz) are predominantly due to electromyographic (EMG) activity (Goncharova et al., 2003). Then, Fc was computed on bipolar channels in such a way that there was no common electrode between all pairs of electrodes in order to avoid massive biases for the functional connectivity analysis (Fp2-F8, F4-C4, P4-O2, T8-P8, Fz-Pz, Fp1-F7, F3-C3, P3-O1, T7-P7).

Functional connectivity was estimated using linear regression analysis which quantifies the dependency of a signal x on a signal y , from signal samples only and independently of the type of relation between the two signals (Pijn and Lopes da Silva, 1993). The level of dependency can be characterized by the linear cross-correlation coefficient r^2_{xy} .

$$r^2_{xy} = \max_{\tau} \frac{\text{cov}^2(x(t), y(t + \tau))}{(\sigma_{x(t)} \sigma_{y(t + \tau)})^2}$$

Where σ and cov denote the standard deviation and the covariance, respectively, and τ the delay between signals x and y . r^2_{xy} will be simply denoted by r^2 in the following.

Correlation values are contained between 0 (y is uncorrelated of x) and 1 (x and y are fully linearly dependent). The estimation of this parameter is performed on a temporal window of fixed duration and sliding in time in order to follow the temporal evolution of the linear statistical relationship between both signals (fixed window of 2s, 1s overlap, max lag of 100 ms). This statistical coupling between

signals was recorded on each pair of the 21 electrodes over the selected resting-state period. In the present study, we summarised coupling at each bipolar electrode pair (node) by the sum of all values containing this node (this is the “node strength” in graph theory terminology). The strength values were computed on signals filtered in the EEG frequency sub-bands followed: theta (4-8 Hz), alpha (8-13 Hz) and beta (13-30 Hz).

2.7 Statistical analysis

Changes in functional connectivity between the first and the last day of each cycle were assessed by linear mixed models (LMM) using the “lme4” package (version 1.1-26, (Bates et al., 2015)) of the statistical software R version 4.0.3 (R Core Team, 2020). One LMM was computed for each frequency band with the responsiveness to the tDCS treatment (R or NR) and cycle as fixed effects. The by-subject intercept was included as a random factor as well as the effect of cycle. Restricted Maximum Likelihood (REML) was used to fit the LMM and Satterthwaite’s method was used to estimate the degrees of freedom. Post-hoc pairwise comparisons were performed with the Least Squares Means (LSM) method. In addition, the difference in seizure onset zones (temporal or extratemporal) and in gender between responder and not-responder patients were tested with Fisher’s exact test. Differences with p-values <0.05 (two-sided) were considered as significant.

3. Results

3.1 Subjects

Ten patients with various forms of focal refractory epilepsy were included in this study between December 2019 and April 2021. Their clinical characteristics are summarized in Table 1.

3.2 Clinical outcome

All patients regularly completed their seizure diary. The results are shown in Figure 3. The mean number (\pm SD) of seizures, in the two months before stimulation, was 44 ± 91 . After the first cycle of tDCS, the average seizure frequency had decreased by -32% ($\pm 44\%$) compared with baseline. After the

second cycle of five days of stimulation, the average seizure frequency had decreased by -57% (± 31) compared with baseline. Finally, after the last cycle (C3) of stimulation, the average seizure frequency had decreased by -48% ($\pm 39\%$). At this point, five patients (50%) had more than 50% decrease in their seizure frequency compared with baseline (R group mean of decrease: $-74\% \pm 14\%$) and were considered as “responders” for the connectivity analysis (see below). The non-responder group (5/10) presented a mean seizure frequency reduction of -16% ($\pm 36\%$) compared to the baseline SF.

No significant difference in responsiveness to the stimulation protocol was found between patients suffering from temporal lobe epilepsy (5/10) and those suffering from extra-temporal lobe epilepsy (5/10) (Odd Ratio=0.5; $p=1$). No significant effect of gender was found on the responsiveness to the treatment (Odd Ratio=0.4; $p=1$). We found no significant difference in the rate of interictal spikes per minute between cycles and the day of stimulation (before the first stimulation of the cycle: "pre" condition and after the last stimulation day of the cycle: "post" condition) ($F_{1,44.084}=0.1012$, $p=0.75$) and between responder and non-responder patients ($F_{1,8.051}=0.2326$, $p=0.6424$).

3.3 Safety and tolerability

Overall, all participants tolerated well tDCS treatment. A slight itching sensation under the stimulation electrodes was described by 7/10 of all patients during stimulation. A sensation of slight dizziness at the beginning of the stimulation was reported by two patients. None of the participants reported moderate nor severe side effects during or after the procedure. Two patients had an increase in seizures: one patient (P8) showed an increase in SF after the first cycle of stimulation (50% increase from baseline) but by the second five-days cycle of stimulation, SF had dropped dramatically from baseline and P8 was considered a responder. Another patient in the non-responder group (P4) showed a moderate and transient increase in SF in the first month following the cycles 2 and 3 (25-50%).

3.3 Functional connectivity

Functional connectivity, estimated by r^2 strength, was first analysed in EEG broadband signal (4-30 Hz). Results did not show a significant change for the cycles ($F_{2,7.1}=0.9$, $p=0.46$) and for responder and non-responder patients ($F_{1,8.1}=0.7$, $p=0.43$) (Fig. 4A). For the theta band (4-8 Hz) analysis, we did not

find a significant change for the cycles ($F_{2,5,9}=1.6$, $p=0.28$) and the responsiveness to the tDCS treatment ($F_{1,8,02}=0.2$, $p=0.65$). However, we clearly identified a tendency to a decrease in the r^2 strength, between the cycles 1 and 3 for the responder patients (Fig. 4B). The alpha band (8-13Hz) analysis revealed no main effect (cycle: $F_{2,5,9}=3.8$, $p=0.09$; response $F_{1,8,3}=0.1$, $p=0.72$) but an interaction effect was present significantly ($F_{2,5,9}=5.9$, $p=0.04$). Post-hoc tests have shown a significant difference between cycles 1 and 2 ($t=2.7$, $p=0.04$) and between 1 and 3 ($t=4.3$, $p=0.009$) for the responder group. The mean strength in responders for the cycle 1 was 0.08 ± 0.09 , in cycle two 0.00 ± 0.07 and -0.06 ± 0.08 for the third cycle (Fig. 4C). The beta band (13-30 Hz) analysis revealed no main effect (cycle: $F_{2,6,8}=0.9$, $p=0.5$; response $F_{1,8,1}=0.05$) but an interaction effect was present significantly ($F_{2,6,8}=6.4$, $p=0.03$). Post-hoc tests have shown a significant difference between cycles 1 and 3 for responder patients ($t=3.4$, $p=0.01$) (Fig. 4D). Although there was no significant difference, we also observed a trend to a decrease in SF between cycles 1 and 2 for responder patients. Interestingly for the non-responder group, we observed a trend for an increase in functional connectivity at the end of the study compared to cycle 1 (non-significant). Finally, comparing Fc at baseline (before any tDCS stimulation), we have found significant difference between responders and non-responders with higher value of r^2 strength in beta band in non-responder patients ($p<0.001$).

4. Discussion

In this open pilot study, we used for the first time a personalized multichannel tDCS protocol targeting the epileptogenic zone as defined on SEEG in a population of patients with drug-resistant focal epilepsy involving different anatomical regions.

4.1 Efficacy of multichannel tDCS

Our study confirms that tDCS can lead to a significant reduction in seizures with a responder rate of about 50% and an average seizure reduction of 48% after the third treatment cycle. In responders, the reduction in seizure frequency was 74% (min -58.5%, max -92%). Importantly, and contrary to previous studies, the duration of patient follow-up (6 months) was longer, and we performed three cycles of tDCS,

whereas in previous studies, only short-term results were reported (Auvichayapat et al., 2013; Fregni et al., 2006; Tecchio et al., 2018). The decrease in seizure frequency observed in our study agrees with previous trials in the field. Most previous studies of tDCS in epilepsy, making use of a generic set-up with a single pair of sponge electrodes, have highlighted the safety and the potential clinical benefit of this neuromodulation technique despite the heterogeneity of patient populations and methods. Three studies by Auvichayapat et al., Tekturk et al., and San-Juan et al. have found a significant reduction in seizure frequency of at least 50% after cathodal tDCS, respectively in patients with epilepsy compared with sham stimulation (Auvichayapat et al., 2013; San-Juan et al., 2017; Tekturk et al., 2016). Another clinical report showed the importance of repeating the DCS session to achieve a cumulative and long-term decrease in seizure frequency (San-Juan et al., 2018). Then, the study by Yang et al., 2019 used a 14-days stimulation protocol versus sham stimulation (Yang et al., 2020). They found a median seizure frequency reduction of 50% and 50% (the first 4-weeks of follow-up), as well as 25% and 45% (the second 4-weeks of follow-up), respectively, for patients who received 20-min of tDCS (group 2) and for patients from the group receiving 2x20-min of tDCS (group 3) as compared to a -12.50% change in the sham group (group 1).

Recently, Kaye et al reported a study using a methodology similar to the present study with regard to optimization (Kaye et al., 2021). There were important differences with our study, however: they used a single cycle of ten days and a 20-minute single stimulation session per day, defining the target area without SEEG, and without using an MRI-personalized brain model in all patients. In our study, we achieved a comparable result in terms of reduction in mean frequency (48% vs. 44%) but with a demonstrated effect over a longer term, using a multi-cycle approach.

Furthermore, the beneficial clinical effect in our study, lasted at least 8 weeks after a 5-days cycle of tDCS. This could be explained by several new factors in our protocol. In addition to SEEG target identification and model personalization, previous studies have shown that the duration of the clinical benefit depends on the repetition, duration, pause between stimulation sessions and current intensity (Monte-Silva et al., 2010; Yang et al., 2020). Yang et al. (2020) have found a greater effect in reducing

seizure frequency using a protocol of 2x20 min stimulation per day with a 20 min interval, compared with a protocol using 40 min stimulation only (no interval) (Yang et al., 2020).

4.2 Personalized tDCS protocol

In the present work, we used an individualized montage targeting the epileptogenic focus identified by the SEEG recordings, which allowed for a more precise delineation of the patient-specific epileptogenic network. Thus, we sought to optimize current levels and orientation such that induced currents maximized inhibitory stimulation of the while minimizing excitatory anodal feedback in other potentially epileptogenic regions from return currents.

4.3 Safety

This long-term study allowed us to confirm the safety of long-term multichannel inhibitory tDCS treatment for epilepsy (6 months). Only mild side effects were reported in most of the participants, such as mild itching and dizziness at the beginning of the stimulation. However, we reported an increase in seizure frequency for one patient in the NR group (25-50%) but who returned to baseline at the end of the study. In addition, one patient in the responder group showed a transient increase in seizure frequency after the first cycle (50%) before a dramatic reduction of seizures after the second and third cycles.

4.4 Functional connectivity

Despite the growing number of studies supporting the clinical interest of applying low-level electric fields using tDCS in epilepsy, the underlying neurophysiological mechanisms remain elusive. Some recent studies have suggested its role regarding transient and long-term effects on cortical excitability (Antal et al., 2017; Cirillo et al., 2017; Lefaucheur and Wendling, 2019; Stagg et al., 2018). Here, we performed a non-invasive measure of functional connectivity to characterize changes induced by several cycles of stimulation. The study of functional connectivity is justified because it is a classic measure of network brain activity and because several publications have shown that regions generating seizures are

characterized by an increased Fc compared to non-epileptic regions (Bettus et al., 2008; Lagarde et al., 2018; Schevon et al., 2007). In the present study, the 6-month period of stimulation had induced a decrease in EEG Fc in responder patients compared to their first cycle of tDCS. This profile of cumulative decrease observed in responders across cycles was not observed for non-responder patients. Conversely, for the latest, we observed a tendency to an increase of Fc at the end of the study. In line with these findings, a recent study has used Fc with fMRI as a quantitative measure of tDCS effects on brain activity in patients with epilepsy (Hao et al., 2021). This study showed that the response to the cathodal tDCS was linked to functional network alterations with a decreasing Fc in patients responding to the active cathodal tDCS.

Here, we observed a general tendency to a decrease in Fc in the broad frequency band in the responder group, but this decrease was only significantly observed for the alpha and the beta bands. In line with our results, Lin and colleagues have shown that seizure reduction due to repeated application of cathodal tDCS was associated with a decrease in phase lag index synchrony measure in the alpha band without altering the number of epileptiform discharges (Lin et al., 2018). The reduction of Fc in epilepsy could be a general mechanism for the action of neuromodulation techniques in epilepsy. A decrease in Fc in responding patients has been shown for example after vagus nerve stimulation (VNS) (Bodin et al., 2015) (Sangare et al., 2020) in delta, after biofeedback (Ferri et al., 2021), or thalamic stimulation (Deutschová et al., 2021). The same trend has been also observed after epilepsy surgery (Ueda et al., 2021).

On the contrary, Tecchio et al have shown that cathodal tDCS was able to increase Fc in six patients suffering from epilepsy in the theta band most specifically (Tecchio et al., 2018). These discrepancies between studies may be partially explained by the repetition of tDCS cycles and the use of different Fc analysis methods.

4.5 Limitations

This study has some limitations. First, our small sample size makes it difficult to generalize results regarding tDCS efficiency for all types of epilepsy disease. Another limitation is related to its open-ended design. We showed that it was possible to obtain a significant response both in terms of seizure frequency and in terms of number of responders (50% of patients with a mean response of -74%) but without comparison with a control group. However, neuromodulation studies, particularly in tDCS, have shown a response to placebo about 13-27% in terms of seizure frequency (Goldenholz and Goldenholz, 2020) and our results are much higher than this figure. Moreover, we have shown that the therapeutic response is linked to an objective marker of functional connectivity. Our estimation of F_c was quite simple based on EEG scalp measurement with a limited number of electrodes. This did not allow us to study more precisely the brain changes induced by the stimulation. One of the emerging issues that remains to be demonstrated is the superiority of a customized multichannel tDCS protocol. Again, a specific study comparing conventional bipolar tDCS and multichannel tDCS could be interesting in the future.

From the modelling perspective there are also several limitations. In this population of patients with scar tissue in the skull due to prior SEEG implantation and, sometimes, surgery, there can be significant changes in the E-field distribution in the brain when compared to a healthy case. This has been shown previously (Datta et al, 2010) and confirmed with our own results (see Supplementary Material). However, in none of these studies have these changes in the modeled induced E-field values exceeded those reported in the literature as inducing lesions in animal model (Bikson et al, 2016). Our own results (see again Supplementary Material) show that when these factors are correctly modelled, the montage optimization algorithm can adjust the currents and electrode positions to account in part for the local increases of E-field under the skull defects. Such models can also be extended to include the effects of implants such as Ti plates (Mercadal et al, 2021a, 2021b). It should be noticed, however, that it is hard to accurately segment accurately the scar tissue with MRI data alone, and the incorporation of CT data with robust segmentation algorithms for scar tissue would improve the models. That uncertainty, allied with the uncertainty on the dielectric properties of the tissues in the scar region remains as a source of uncertainty when predicting the E-field distribution in this population of subjects.

5. Conclusions

This pilot study shows the feasibility, clinical efficiency and safety of a long-term (>6 months) multichannel cathodal tDCS with a personalized stimulation protocol in patients with drug-resistant epilepsy. We observed a substantial reduction in seizure frequency after three cycles of 5-days stimulation every two months. Half of the patients were responders with a mean seizure reduction of 74%. This clinical improvement for these difficult cases is cumulative with the stimulation cycles and was associated with a decrease in functional connectivity in alpha and beta bands.

Funding

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Declaration of Competing Interest

The non-invasive brain stimulation device used in this study was produced by Neuroelectrics Corp. and Starlab Neuroscience. Dr. Giulio Ruffini is a co-founder of these companies, Dr. Ricardo Salvador and Dr Maria Chiara Biagi works for this company. All the other authors state there is no conflict of interest.

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Table and Figure legends

Table 1: Patient data. *Abbreviations: SOZ: Seizure onset zone; SEEG: Stereoelectroencephalography; SMA: Supplementary motor area; SZs: Seizures; FCD: Focal cortical dysplasia; SGTC: Seizure generalized tonico-clonic; ASM: Antiseizure medication; R: responder; NR: Non-responder.*

Fig. 1. Study timeline. For each patient, the information of the seizure diary was collected at each timepoint (M1C1, M2C1, M1C2, M2C2, M1C3, M2C3). Each cycle was composed of 5 days of two periods of 20 minutes stimulation separated by 20 minutes off (20 min tDCS – 20 min off – 20 min tDCS) with a 1-hour EEG performed before the first day of stimulation and right after the last day of the cycle. Each session was renewed every two months. *Abbreviations: tDCS: transcranial direct current stimulation; EEG: Electroencephalography; M-2, M-1: 1 and 2 months before the first stimulation cycle; M1C1: one month after the first cycle; M2C1: two months after the first cycle; M1C2: one month after the second cycle; M2C2: two months after the second cycle; M1C3: one month after the third cycle; M2C3: two months after the third cycle.*

Fig. 2. Example of epileptogenic zone identification using SEEG recordings for tDCS targeting using the optimization protocol of tDCS electrode's montage for the patient 5. A. SEEG recordings during left temporal lobe ictal event. Seizure starts from left temporo-basal area and left occipito-temporal area. Intra-cerebral electrodes are identified by letter (A, etc.) and the recordings' leads are numbered from 1 to 15, low numbers corresponding to the deepest structures (for example, leads TB' 1–2 recorded the electrical activity of the entorhinal cortex). TP': left temporal pole electrode, TB': left temporo-basal electrode; GPH' left parahippocampal gyrus electrode, OT': left occipito temporal electrode; T' left superior temporal electrode; H' Heschl gyrus electrode. GC': electrode reaching the posterior cingulate gyrus. Bipolar signals are obtained by subtracting the signals recorded from two adjacent leads. B. The maximum epileptogenicity values (red sphere) are shown in a three-dimensional scheme of the patient 5 brain illustrated based on CT-MRI reconstruction of electrode tracks and

epileptogenic index (EI). EI values were computed on a bipolar montage derivation. The diameter and position on the color scale are proportional to the normalized EI values. C. Optimization protocol used for patient 5 with tDCS electrode's positions and generated normal component of electrical fields (V/m). The blue area (left panel) corresponds to the epileptogenic zone and must be inhibited with cathodal electrodes (in blue below). The red part (right panel) is the area with the excitatory return current using anodal electrodes (in red below). *Abbreviations: tDCS: transcranial direct current stimulation; SEEG: stereoelectroencephalography.*

Fig. 3. Evolution of seizure frequency over time after three stimulation cycles of responder and non-responder patients. A. Evolution of seizure frequency for responder patients (N=5). B. Evolution of seizure frequency for non-responder patients (N=5). Y axis: percentage of SF evolution compared with baseline (%). X axis: time periods. *Abbreviations: M1 after C1: one month after the first cycle; M2 after C1: two months after the first cycle; M1 after C2: one month after the second cycle; M2 after C2: two months after the second cycle; M1 after C3: one month after the third cycle; M2 after C3: two months after the third cycle; SF: seizure frequency.*

Fig. 4. Multichannel cathodal tDCS induced a decrease in functional connectivity for responder patients in alpha (8-13 Hz) and beta (13-30 Hz) bands. Variation of Fc across cycles (6 months in total) calculated by the difference in strength before and after each cycle of 5 day's stimulation (D5-D1) in broadband filtered (4-30 Hz) (A), in theta (4-8 Hz) (B), in alpha (8-13 Hz) (C), and beta (13-30 Hz) (D) bands for non-responder and responder patients. *Abbreviations: Strength D5-D1: Strength Day 5 – Strength Day 1 (after – before tDCS cycle); tDCS: transcranial direct current stimulation; Fc: functional connectivity.*

Figure 1

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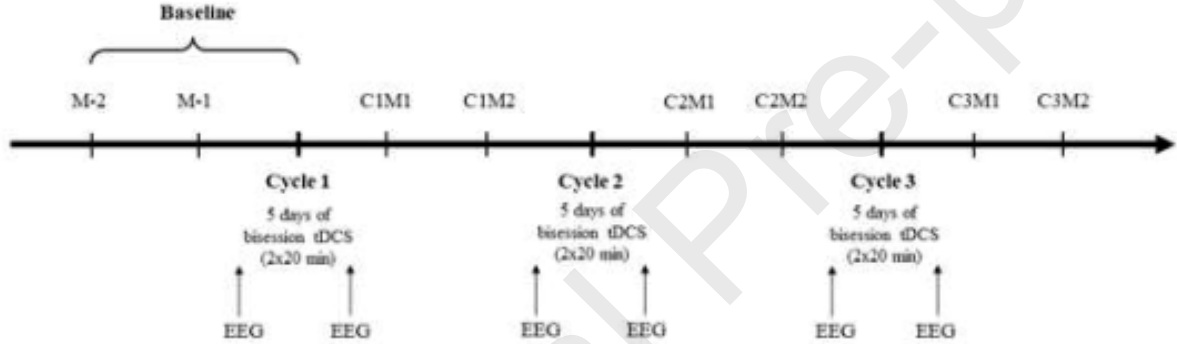


Figure 2

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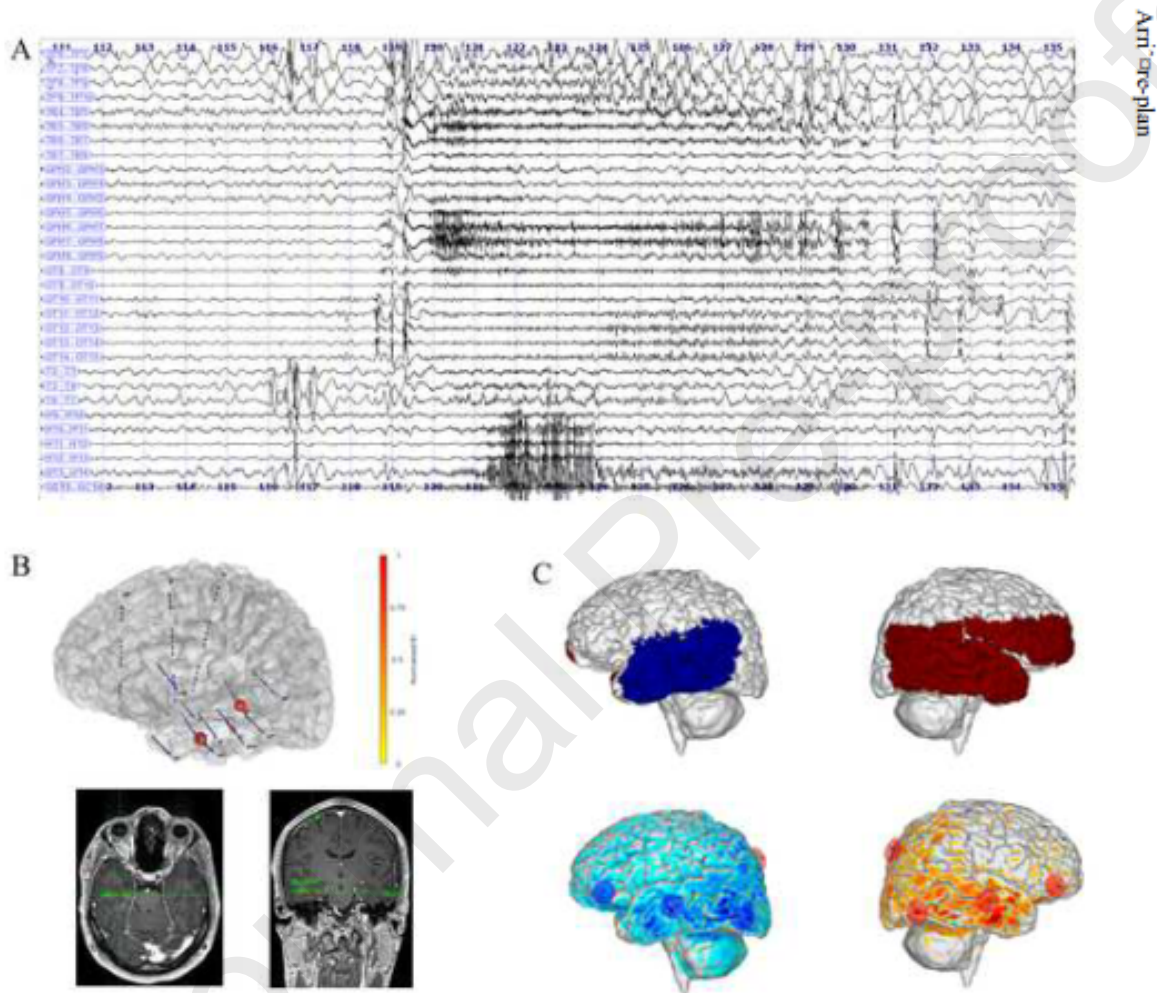


Figure 3

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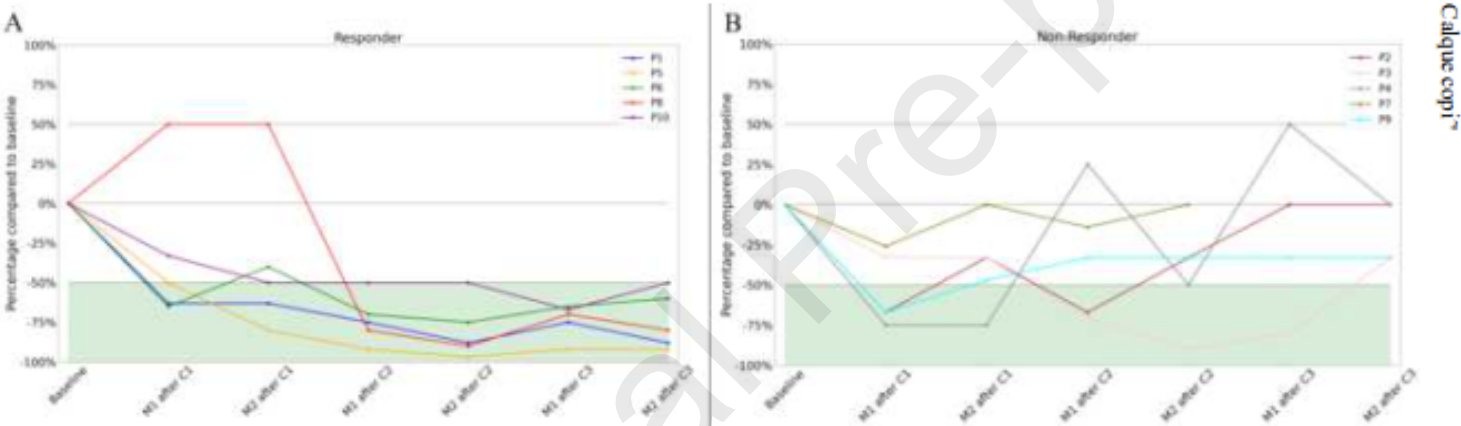
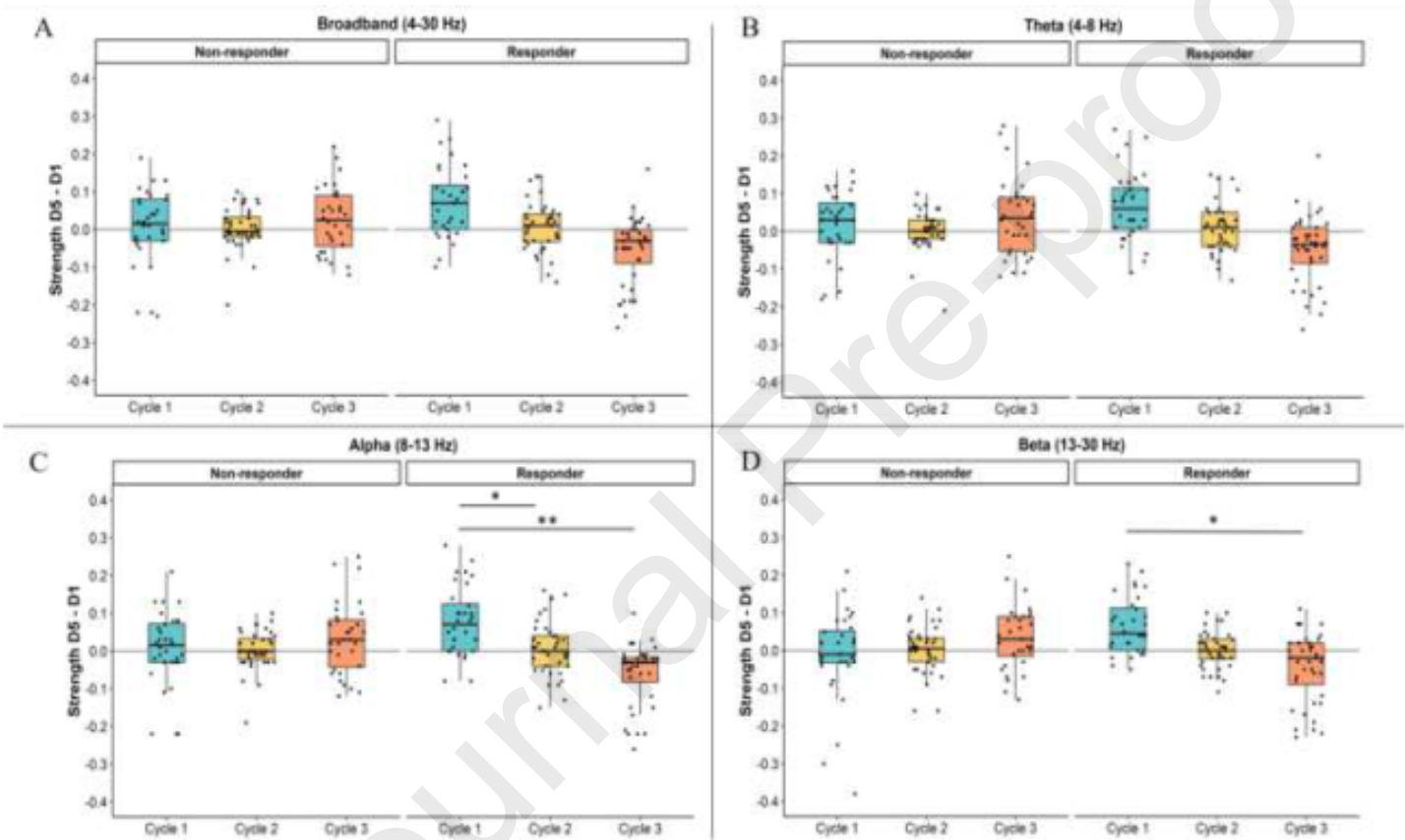


Figure 4

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| Patient | Gender | Age | SOZ defined by SEEG | SEEG electrodes (number) | Etiology | SZs type | ASM | Previous failed Surgery | tDCS target | Injected current (mA) | Desired E field in target (V/m) | Achieved average E field in target (V/m) | Number of electrodes | Response |
|---------|--------|-----|---|--------------------------|-----------------|---|-----|--------------------------------------|--|-----------------------|---------------------------------|--|----------------------|----------|
| 1 | F | 12 | Left paracentral lobule, Post SMA | 8 | Unknown | EPC, focal motor seizures | 2 | Premotor Cortectomy | Left paracentral | 1.99 | 0.5 | -0.070 | 8 | R |
| 2 | M | 60 | Left temporal lateral, mesial, Parietal infero-temporal | 15 | Infectious | Focal non motor, impaired awareness | 3 | No | Left temporo-basal | 1.99 | 0.25 | -0.016 | 8 | NR |
| 3 | M | 34 | Right parietal posterior, Precuneus, cuneus | 9 | Unknown | Focal non motor, SGTC | 5 | No (thermocoagulation) | Right posterior parietal | 1.99 | 0.5 | -0.011 | 6 | NR |
| 4 | M | 23 | Left temporal lateromesial | 9 | FCD | Focal non motor | 2 | Anterior anterior temporal lobectomy | Left temporo insular | 1.99 | 0.5 | -0.031 | 7 | NR |
| 5 | M | 41 | Left basal, lateral temporal | 16 | Unknown | Focal non motor, partial impaired awareness | 2 | No (thermocoagulation) | Left temporo-opercular | 1.99 | 0.5 | -0.017 | 7 | R |
| 6 | F | 29 | Left latero-mesial, Temporo-occipital | 13 | FCD | Focal non motor | 3 | No (thermocoagulation) | Left temporal | 1.99 | 0.25 | -0.008 | 7 | R |
| 7 | M | 20 | Right operculo-insular | 9 | Unknown | Focal sensitivi-motor, visual hallucination | 3 | Temporal lobectomy Operculectomy | Left temporo perylvian, Mesial occipital | 1.99 | 0.5 | -0.038 | 8 | NR |
| 8 | M | 29 | Left parietal, premotor | 12 | Prenatal stroke | Focal motor, impaired awareness | 4 | Left parietal cortectomy | Left fronto parietal sup | 1.99 | 0.25 | -0.023 | 7 | R |
| 9 | F | 38 | Left temporo-latero-mesial | 9 | FCD | Focal motor, impaired awareness | 3 | Anterior temporal lobectomy | Left temporal | 1.99 | 0.5 | -0.070 | 7 | NR |
| 10 | M | 14 | Right paracentral | 10 | Unknown | Focal motor, no impaired awareness | 4 | No | Right paracentral | 1.99 | 0.5 | -0.042 | 7 | R |