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# A Controlled Clinical Trial of Cathodal DC Polarization in Patients with Refractory Epilepsy

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**Summary:** *Purpose:* To study the effects of cathodal DC polarization in patients with refractory epilepsy and malformations of cortical development (MCDs) as indexed by seizure frequency and epileptiform EEG discharges.

*Methods:* Nineteen patients with MCDs and refractory epilepsy underwent one session of DC polarization (20 min, 1 mA) targeting the epileptogenic focus. The number of epileptiform discharges (EDs) in the EEG and seizures were measured before (baseline), immediately after, and 15 and 30 days after either sham or active DC polarization. Seizure frequency after the treatment was compared with baseline.

*Results:* Active compared with sham DC polarization was associated with a significant reduction in the number of epileptiform discharges [mean ED reduction of −64.3% (95% CI, −122.5% to −6.0%) for the active treatment group and −5.8% (95% CI, −26.8% to 15.2%) for the sham treatment group]. A trend ($p = 0.06$) was noted for decrease in seizure frequency after active compared with sham treatment [mean seizure frequency decrease of −44.0% (95% CI, −95.0% to 7.1%) for the active treatment group and −11.1% (95% CI, −22.2% to 44.4%) for the sham treatment group].

*Conclusions:* This randomized, controlled study shows that cathodal DC polarization does not induce seizures and is well tolerated in patients with refractory epilepsy and MCDs. Furthermore, the results suggest that this technique might have an antiepileptic effect based on clinical and electrophysiological criteria. **Key Words:** Cathodal DC polarization—Transcranial direct current stimulation—EEG—Epilepsy—Malformations of cortical development.

Modification of dysfunctional electrical brain activity by using electrical stimulation seems to be a potentially valuable alternative for epilepsy treatment that should be further explored. For instance, evidence exists that direct stimulation of subcortical and cortical mesotemporal structures can reduce seizure frequency in some forms of epilepsy (1,2). A few animal (3) and human studies (4–6) suggest that noninvasive low-frequency repetitive transcranial magnetic stimulation (rTMS) might also be clinically effective in seizure control in patients with refractory epilepsy. DC polarization provides an alternative means of modifying brain excitability noninvasively, and its effects on the cortical excitability appear to be similar to those of rTMS (7–10). Furthermore, animal studies showed that direct-current (DC) stimulation can indeed induce a local suppression of the epileptiform activity (11–13). A number of studies using DC polarization in humans suggest that this technique is safe (14–17). In DC polarization, the cerebral cortex is stimulated through a weak constant electric current in a noninvasive and painless manner. This weak current induces focal changes of cortical excitability—increase or decrease depending on the electrode polarity—that last beyond the period of stimulation. Several studies have shown that this technique might modulate cortical excitability in the human motor (18–20), prefrontal (21), and visual cortex (17,22).

Therefore we hypothesized that DC brain polarization might also have an antiepileptic effect in patients with malformations cortical of development (MCDs) and medically refractory epilepsy. The aims of the present study were (a) to establish preliminary information for future trials about the effects of DC polarization in patients with MCDs and refractory epilepsy, and (b) to address the question of whether DC polarization might cause electrophysiologic changes (as indexed by EEG) in patients with MCDs and refractory epilepsy. We decided to study patients with MCDs as this pathology represents an important etiology of refractory epilepsy and, therefore, a common cause of referrals for epilepsy surgery. However,

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a large proportion of patients with multifocal MCDs and those with lesions in eloquent cortex are poor surgical candidates. Such patients represent a challenge for treatment and a focus of continuous interest for alternative therapeutic approaches.

To our knowledge, no studies have applied DC polarization in patients with refractory epilepsy to date; therefore we report the first study investigating the electrographic and clinical response to DC polarization in 19 patients.

## METHODS

### Patients

Patients were prospectively and sequentially selected from a specialized epilepsy clinic if they fulfilled the following criteria: (a) diagnosis of MCDs based on magnetic resonance imaging (MRI); (b) refractory epilepsy as defined by the occurrence of monthly seizures, on average, during the preceding year, despite the use of two or more antiepileptic drugs (AEDs) in adequate doses; (c) nonsurgical candidacy defined by surgical contraindications (i.e., more than one MCD lesion or patients' refusal to surgical treatment); and (d) compliance with AED treatment for the preceding year. Nineteen patients (mean age, 24.16 $\pm$ 7.9 years, mean $\pm$ SD) participated in the study and were randomly assigned to one of two treatment groups. All patients but two (one in each group) had very frequent or continuous epileptiform discharges (EDs) on EEG. All patients continued their AEDs as prescribed by their treating physicians. The general clinical characteristics of the patients are summarized in Table 1.

The study was performed in accordance with the Declaration of Helsinki (1964). Written informed consent was obtained from all participants before inclusion in the study, which was approved by the local ethics committee (University of Sao Paulo).

**TABLE 1.** *Demographic and epilepsy baseline characteristics*

| | Sham treatment | Active treatment | p Value |
|---|---|---|---|
| Gender [number (%)] | | | |
| Male | 6 (66%) | 5 (50%) | 0.65 |
| Female | 3 (33%) | 5 (50%) | |
| Age: mean (SD) | 24.0 (9.8) | 24.3 (6.4) | 0.92 |
| Seizure frequency/28 days [baseline mean (SD)] | 8.4 (5.6) | 7.2 (3.6) | 0.75 |
| Concomitant AEDs (number of patients) | | | |
| 0 | 0 | 0 | 0.62 |
| 1 | 0 | 0 | |
| 2 | 7 | 6 | |
| 3 | 2 | 4 | |
| Lesions (cortical dysplasias) | | | 0.44 |
| Polymicrogyria | 5 | 6 | |
| Heterotopia | 4 | 2 | |
| Other dysplasias | 0 | 2 | |

Student's *t* test for the continuous variables and Fisher's exact test for the categoric variables were performed.

### Experimental protocol

Patients selected in the outpatient service that satisfied the inclusion criteria and accepted participation in this protocol were included in this study. These patients were randomized into two groups: real and sham DC polarization. These patients were instructed to record the number of seizures in a calendar during the month before the treatment. Furthermore, they were instructed not to change their AED doses throughout the study. Patients were blinded for the treatment received, and no protocol violations occurred, except for one patient who was admitted to the ICU owing a severe pneumonia (this patient received sham treatment).

### Epileptiform discharges

All patients underwent 18-channel EEG recording before, immediately after, as well as 15 and 30 days after DC polarization application. Patients were kept awake during this procedure to control the effects of sleep on ED frequency. The total duration of each EEG was 20 min. Initially each EEG recording was inspected visually, and all segments containing eye movements or muscle activity were rejected. We therefore counted the number of EDs for the total duration of the artifact-free EEG. EDs were counted in all derivations and not only in the epileptogenic focus. The EEG analysis was performed by clinical neurophysiologists (S.T.S. and K.D.V.) who were blinded with regard to the timing of the EEG relative to DC polarization and to treatment arm (active or placebo).

The EEG also was used to measure the safety of this treatment. Therefore the EEG recordings also were analyzed with regard to the occurrence of afterdischarges immediately after the stimulation, ictal activity, and changes in the pattern of interictal discharge compared with the baseline period.

### Clinical outcome

Subjects and their relatives were asked to record seizures on a calendar during the month before and the month after the treatment. By using these calendars, we counted the number of seizures for two different periods (baseline, the month before DC polarization treatment; and posttreatment, 1 month after treatment). We also evaluated the distribution of seizures across the evaluation period (i.e., to assess whether a uniform distribution of the seizures occurred during the posttreatment period).

Patients were asked to report any abnormal sensation such as those typically experienced during auras or complex partial seizures during and immediately after the stimulation. Patients were observed by a trained neurologist during the stimulation and for 3 h after treatment. Any abnormal behavior suggesting epilepsy was recorded.

**TABLE 2.** *Electrodes position and seizure reduction*

| | Pt | Lesion/EEG | Anode electrode | Cathode electrode | Seizure reduction[b] | Epileptiform discharge reduction[b] |
|---|---|---|---|---|---|---|
| Active | 1 | Multifocal | T4 | Cz | 0.86 | 0.63 |
| | 2 | Focal | T6/T5[a] | F3/F4[a] | 0.00 | 0.94 |
| | 3 | Focal | Left/Right supraorbital[a] | T6/T5[a] | 0.00 | 0.60 |
| | 4 | Focal | Left supraorbital | T4 | 0.40 | 0.77 |
| | 5 | Focal | T5 | Fp2 | 0.95 | 0.56 |
| | 6 | Focal | T5 | F8-T4 | 0.75 | 0.40 |
| | 7 | Focal | Left/Right supraorbital[a] | T3-T5/T4-T6[a] | −0.40 | 0.44 |
| | 8 | Focal | Left supraorbital | F8-T4 | 0.00 | 0.33 |
| | 9 | Focal | Right supraorbital | T3 | 0.86 | 0.99 |
| | 10 | Focal | T5 | F4 | 0.75 | 0.1 |
| Sham | 11 | Multifocal | Right supraorbital | Cz | 0.13 | −0.73 |
| | 12 | Focal | Left supraorbital | T6-O2 | 0.00 | −0.02 |
| | 13 | Focal | Right/Left supraorbital[a] | T5-01/T6-O2[a] | 0.25 | −0.20 |
| | 14 | Multifocal | Right supraorbital | Cz | −1.00 | −0.08 |
| | 15 | Focal | T5 | F4 | 0.00 | 0.30 |
| | 16 | Focal | Right supraorbital | T3 | 0.00 | 0.15 |
| | 17 | Focal | Right supraorbital | C3 | 0.00 | −1.00 |
| | 18 | Focal | T3 | P4 | 0.00 | 0.25 |
| | 19 | Focal | Left supraorbital | T6 | −0.13 | 0 |

[a]As these patients had two epileptogenic foci, both hemispheres were stimulated (10 min each hemisphere).
[b]Compared to baseline, a negative number indicates an increase in seizure frequency and ED.

During the recruitment and informed-consent process, patients were told that DC polarization could improve or worsen their epilepsy. Furthermore, they were told that the effects of this treatment, if any, would be short-lived. All patients were told that the primary aim of the study was to investigate the safety of DC polarization.

### Transcranial direct current stimulation

Direct current was transferred by a saline-soaked pair of surface sponge electrodes (35 $cm^2$) and delivered by a specially developed, battery-driven, constant-current stimulator (Schneider Electronic, Gleichen, Germany) with a maximum output of 10 mA. The site for stimulation was determined according to the EEG electrode 10–20 system. Because cathodal stimulation decreases cortical activity, we placed the cathode electrode over the epileptogenic focus according to EEG baseline. The anode electrode was placed over a silent area (i.e., without epileptogenic activity; see Table 2). The silent area was defined as the area with normal EEG activity or the area with the smallest amount of epileptogenic activity. In case of a multifocal epileptogenic activity (see Table 2, three patients), we placed the anode electrode over the contralateral supraorbital area (unless the epileptogenic activity was important in this area as well) and the cathode electrode over Cz. In four patients with bilateral lesions and EDs (three in the active and one in the sham DC polarization group), we stimulated two areas that seemed to be equally epileptogenic on EEG. A constant current of 1-mA intensity was applied for 20 min (voltage varied from 8.5 to 14.9V across subjects). Subjects felt the current as an itching sensation at both electrodes in the beginning of the stimulation. For the sham stimulation, the electrodes were placed in the same position; however, the stimulator was turned off after 5 s as previously described (23). Therefore the subjects felt the same initial itching sensation, but received no current for the rest of the stimulation period. This procedure allowed us to blind subjects for the respective stimulation conditions (16). Indeed, when asked, immediately after the experiment, if the stimulation was sham or active, the subjects failed to answer correctly, responding, in all the cases, that the stimulation was active, perhaps because of the itching sensation that both types of stimulation caused.

### Data analysis

The effects of DC polarization were analyzed by comparing seizure frequency and epileptiform discharges between baseline and posttreatment. Analyses were done with SAS statistical software (version 8.0; Cary, NC, U.S.A.). We used a two-way analysis of variance (ANOVA) model with repeated measures on time. For this model, we used two factors (Group, between-subjects factor, and Time of evaluation, within-subjects factor). Therefore the main effects of Group and Time, and the interaction of Group × Time were calculated. As we were interested to evaluate primarily whether the application of DC polarization would cause immediate changes in the EEG, we initially performed an analysis including two time periods: before and immediately after the stimulation. Subsequently, in an exploratory analysis (not correcting the p value), we investigated whether the effects of DC polarization on the EEG would last more than the immediate period of evaluation. Therefore we performed a further two-way ANOVA, but, at this time, with four different time points (baseline, immediately after, and after 15 and 30 days of stimulation). For the number of

seizures, we analyzed, first, the change in the mean number of seizures between baseline and poststimulation by using a two-way ANOVA with repeated measures on time. When appropriate, post hoc comparisons were carried out by using Fisher LSD correction for multiple comparisons. Data are reported as mean and 95% confidence intervals (95% CIs) or standard deviation. Statistical significance refers to a two-tailed p value $<0.05$.

## RESULTS

Patients tolerated the DC polarization treatment well. No adverse effects and no complex partial seizures or secondarily generalized seizures occurred within 3 h after the stimulation. Table 1 describes the patients' characteristics divided by treatment group. No significant difference was found in the baseline characteristics between these two treatment groups.

### Epileptiform discharges

We did not find ictal activity on the EEG after DC polarization in any of the patients. Furthermore, no changes (compared with baseline) were found in the pattern of the interictal discharges in the posttreatment EEG to suggest an ictal or postictal period.

We hypothesized that cathodal DC polarization would induce a decrease in cortical excitability and therefore would result in a reduction in the number of epileptiform discharges in the EEG. A two-way (two factors: Group and Time) repeated-measures (on Time) ANOVA showed no Group effect (between-subjects effect, $F = 0.04$; $df = 1, 17$; $p = 0.84$), but a significant Time (within-subjects effect, $F = 6.59$; $df = 1, 17$; $p = 0.02$) and interaction term (Group $\times$ Time) effect ($F = 4.49$; $df = 1, 17$; $p = 0.049$). Although the p value for the interaction term was only marginally significant, the absolute values show a remarkable decrease in the number of EDs. Patients who received active DC polarization had a decrease in the mean number of EDs from $413.9 \pm 427.1$ (baseline) to $148.0 \pm 168.2$ (after stimulation), whereas patients who received sham DC polarization had a small decrease in EDs from $334.4 \pm 619.5$ to $315.0 \pm 632.5$ (Fig. 1). Therefore the marginally significant p value reflects the large variance of these data, as the number of EDs is largely variable across patients. The mean and 95% CI for the difference in EDs between immediately after and baseline was $-265.9$ ($-507.1$ to $-24.69$) for the active DC polarization group and $-19.4$ ($-89.8$ to 50.9) for the sham DC polarization group.

In an exploratory analysis, we investigated the long-lasting effects of DC polarization on the cortical excitability of these patients. We then performed a two-way (Group factor: active and sham; and Time factor: four time points) repeated-measures (on Time) ANOVA. This analysis disclosed similar results compared with the previous analysis: a nonsignificant effect of Group of stimulation (between-subjects effect, $F = 0.09$; $df = 1, 17$; $p = 0.77$), a significant Time effect (within-subjects effect, $F = 3.2$; $df = 3, 51$; $p = 0.03$) and a statistical trend for the interaction term (Group $\times$ Time) effect ($F = 2.6$; $df = 3, 51$; $p = 0.06$). Similarly, the large variance of these data decreased the significance of this test (see Table 3). Although not significant, these data suggest that the effects of the DC polarization on the cortical excitability might last several days (Fig. 1).

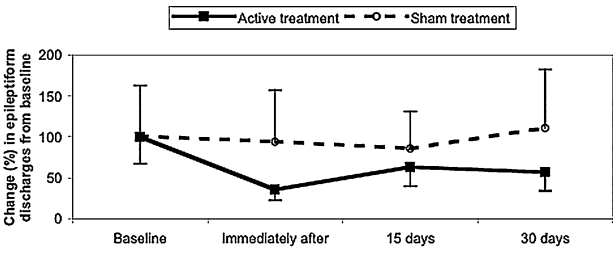


**FIG. 1.** Change (percentage) in epileptiform discharges from baseline (data were normalized: 100% represents baseline for both groups). Immediately after stimulation, a significant reduction in the epileptiform discharges in the active treatment group occurred compared with the sham-treatment group. Error bars indicate SEM (standard error of the mean).

To evaluate whether anodal stimulation was associated with an increase in the number of EDs in the site of stimulation, we performed a new analysis in which we included only the number of EDs in the position of the anodal electrode. For the supraorbital stimulation, we evaluated Fp1/Fp2. This new analysis showed that a small decrease occurred in the number of EDs ($-4.95\%$) after active DC polarization that was not significant when compared with sham treatment ($p = 0.97$; see Table 4).

### Seizure frequency

We evaluated the number of the adverse events and compared seizure frequency between baseline and the period after DC polarization. Few adverse events occurred, and they were related to the mild itching of the site of stimulation (three patients in the active group and one patient in the sham DC polarization group). No seizures occurred during or within 3 h of DC polarization application. None of the patients reported an increase in seizure frequency after the treatment in the active-treatment group. Furthermore, the analysis of seizure distribution in the posttreatment period (1 month of evaluation) showed that they were not concentrated in the period after the stimulation, but were uniformly distributed.

To analyze whether the stimulation was associated with an increase in the number of seizures, we performed a two-way (Group and Time of stimulation) repeated-measures (on Time) ANOVA. This analysis revealed no Group effect (between-subjects effect; $F = 0.28$; $df = 1, 17$; $p = 0.6$), no Time effect (within-subjects effect; $F = 2.01$; $df = 1, 17$; $p = 0.17$), but a trend for the interaction term (Group $\times$ Time) effect ($F = 4.04$; $df = 1, 17$; $p = 0.06$). The

**TABLE 3.** *Follow-up evaluation of the epileptiform discharges*

| Group | EEG1 (baseline) | EEG2 (immediately after) | EEG3 (15 days) | EEG4 (30 days) |
|---|---|---|---|---|
| Active treatment (mean ± SD) | 413.9 (±427.1) | 148.0 (±168.2) | 262.3 (±310.2) | 236.0 (±297.1) |
| Sham treatment (mean ± SD) | 334.4 (±619.5) | 315.0 (±632.5) | 288.3 (±449.2) | 371.3 (±714.3) |

interaction term indicates that the effect of Time depended on the group of stimulation. The mean number (±SD) of seizures, in the month before stimulation, was 8.4 ± 5.6, and, in the first month after stimulation, 4.7 ± 5.3, for the active-treatment group, and 7.2 ± 3.5 and 8.0 ± 5.2, respectively, for the sham-treatment group. The mean and 95% CI for the difference in the number of seizures before and after the treatment was −3.7 (−7.9 to 0.6) for the active-treatment group and 0.8 (−1.6 to 3.2) for the sham-treatment group (Fig. 2).

As the anodal stimulation is associated with an increase in the cortical excitability, a concern was present that this treatment would increase EDs in patients with multifocal EDs in the EEG or lesions in the MRI. Three patients with multifocal abnormalities were included in this study (two of them received sham and the other received active stimulation). The patient that received active stimulation did not have an increase in the seizures or EDs after stimulation; on the contrary, this patient had a decrease in seizures and EDs after treatment (Table 2).

Because patients in our study had different characteristics regarding their lesions (i.e., some patients had a single epileptogenic focus, and others had two or multiple epileptogenic foci), and thus the corticosubcortical network effects of this treatment may differ across patients, we performed an additional analysis in which we compared the effects of active DC polarization across three different groups of patients. Therefore we divided these patients into three groups and calculated the mean seizures and ED reduction for each group: group 1 (one patient), multifocal abnormalities (seizure reduction, 86%; ED reduction, 63%); group 2 (six patients), single focal abnormality (mean seizure reduction, 62%; mean ED reduction, 52.5%); and group 3 (three patients), two epileptogenic foci, bilateral stimulation (mean seizure reduction, −13.3%; mean ED reduction, 66%). We compared the group with a single focus (group 2) with the group with bilateral foci (group 3) and found that patients in group 2 had a significantly larger decrease in seizure reduction compared with group 3 ($p = 0.013$), but no difference was found for ED reduction ($p = 0.54$). In addition, we performed the same analysis for the sham group, with group 1 (two patients), multifocal abnormalities (mean seizure reduction, −43.5%; mean ED reduction, −40.5%); group 2 (six patients), single focal abnormality (mean seizure reduction, −2.1%; mean ED reduction, −5.3%); and group 3 (one patient), two epileptogenic foci, bilateral stimulation (seizure reduction, 25%; ED reduction, −20%). We then compared subgroups 1 (multifocal abnormalities) and 2 (single focal abnormality) and found no significant

**TABLE 4.** *Change in the number of epileptiform discharges in the anode electrode*

| Active treatment | | Sham treatment | | |
|---|---|---|---|---|
| Patient | Change in ED[a] | Patient | Change in ED[b] | p Value |
| 1 | 0.52 | 11 | 0.20 | 0.97 |
| 2 | 0.33 | 12 | −0.32 | |
| 3 | 0 | 13 | 0 | |
| 4 | 0 | 14 | 0.33 | |
| 5 | 0 | 15 | 0 | |
| 6 | −0.29 | 16 | 0 | |
| 7 | 0 | 17 | 0 | |
| 8 | −0.47 | 18 | −0.69 | |
| 9 | 0 | 19 | 0 | |
| 10 | −0.58 | | | |
| Mean | −0.049 | | −0.054 | |
| SD | 0.36 | | 0.30 | |

[a]Difference between before and immediately after stimulation: a negative change indicates a decrease in the number of epileptiform discharges (EDs).

[b]Unpaired *t* test. Note that, in most of the cases, 0 change indicates that the patient had 0 EDs before and after stimulation as the anodal electrode was placed over the silent area.

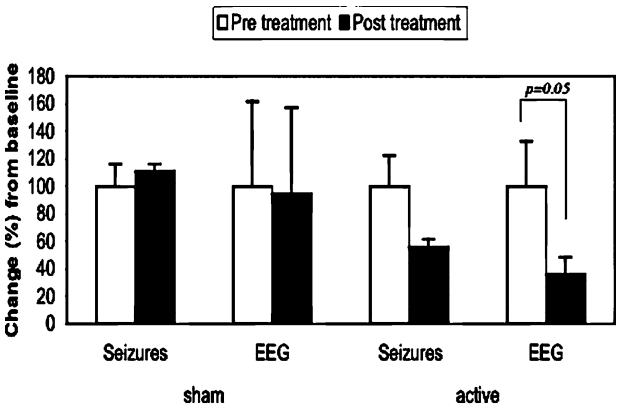


**FIG. 2.** Comparison of epileptiform discharges and seizure frequencies between pretreatment (white column) and posttreatment (black column) in the sham- and active-treatment (DC polarization) groups. Note that data were normalized (100% represents baseline for both groups), and posttreatment is represented as a change from the baseline. Error bars indicate SEM (standard error of the mean).

difference in seizure frequency ($p = 0.17$) and in EDs ($p = 0.40$) between these two sham subgroups. Finally we compared the results between the largest sham and active subgroup, the single focal abnormalities group, and found a significant difference in the seizures frequency ($p = 0.001$) and EDs ($p = 0.03$) between these two subgroups. This exploratory analysis suggests that active cathodal DC polarization in patients with single focal abnormalities was significantly effective in seizure and epileptiform reduction compared with the similar group of patients that received sham treatment.

To evaluate whether the medications that these patients were taking were associated with the outcome, we performed a linear regression model in which the dependent variable was either the seizures or ED reduction and the independent variables were carbamazepine (CBZ; total dosage), benzodiazepine (BZD; equivalent units), lamotrigine (LTG; total dosage), valproate (VPA; total dosage), and total amount of medication (considering standard dosages for each medication). This new model including treatment (active or sham) and one of the variables mentioned (this model permitted the inclusion of only two variables because of the small sample size of our study) showed, for the ED and seizure-reduction models, respectively, that the following medications were not significantly correlated to the outcome: VPA ($p = 0.78$ and $p = 0.77$); CBZ ($p = 0.96$ and $p = 0.92$) and LTG ($p = 0.34$ and $p = 0.35$), whereas a significant (or a trend toward a significant) correlation existed for the following variables: BZD ($p = 0.010$ and $p = 0.075$) and total amount of medications ($p = 0.076$ and $p = 0.078$). The beta coefficient for BZD for the ED model was 0.04, indicating that 1 unit change of BZD was associated with an increase of 5% in the magnitude of the effects (i.e., reduction in ED). Therefore cathodal DC polarization might have an add-on effect on certain medications, such as BZDs, to control seizure frequency; but this finding must be further replicated, as this was an exploratory analysis.

Finally, a descriptive individual analysis of the patients suggested that no difference existed in the results across patients stimulated with different electrode montages and with different types of lesions (Table 2).

## DISCUSSION

This randomized, sham-controlled study provides evidence that cathodal DC polarization does not increase (but it might decrease) seizure frequency. Furthermore, our findings show that DC polarization can modulate the activity of the epileptogenic focus in these patients, as it decreased the number of epileptiform EEG discharges.

The results suggest that cathodal DC polarization decreased cortical excitability in the epileptogenic focus of MCD patients. This is in line with the proposed mechanism of action for DC polarization: a polarization shift in the stimulated area (i.e., a hyper- or depolarization that depends on the stimulation polarity). Since the study published by Bindman et al. (1964), several authors have demonstrated in humans that whereas cathodal stimulation decreases cortical excitability, anodal stimulation increases it (15,24,25). In this study, the findings suggest that cathodal DC polarization might have induced a hyperpolarization of the epileptogenic focus, thus suppressing epileptic activity. This result is in agreement with past research that showed that direct current stimulation can suppress the epileptiform activity in rat hippocampus in vitro (11).

As DC polarization increases the cortical excitability over the area that is stimulated with the anode electrode, this raises concerns about the safety of this technique in patients with epilepsy. However, we failed to show that active treatment is associated with an increase in the number of seizures, when the anode electrode is placed distant from the epileptogenic focus, in a silent area. Furthermore, we showed no significant increase of EDs in the area of the anodal stimulation. Although this finding might at the first glance be paradoxical, as anodal stimulation is associated with an increase of cortical excitability, three main reasons might explain the lack of ED increase after anodal stimulation:

1. We chose a silent area in terms of EDs to place the anode electrodes. Thus the area that received anodal stimulation was placed distant from the primary epileptogenic focus (except for one patient with multifocal abnormalities). Because the functional effects of DC polarization are largely restricted to the area under the electrode (8), it is not likely that excitability enhancement anodal DC polarization situated far from the primary epileptogenic focus influences epileptic discharges, although it might influence focal cortical excitability. For most of the patients, the frequency of EDs before and after stimulation (at the position of anode electrode) was 0. This provides further evidence that DC polarization does not provoke seizures if an appropriate electrode montage is pursued.
2. Even if anodal stimulation was associated with a focal increase in cortical excitability; this excitability enhancement was not translated as an increase in the ED frequency, because anodal stimulation was performed over an area of relatively normal (or least affected) brain activity.
3. Another possible reason that anodal stimulation was not associated with an increase in the frequency of EDs in these patients was that most of these patients received CBZ. It has been shown that this drug inhibits the excitability-enhancing effect of

anodal stimulation during and after DC polarization. Conversely, this drug does not modify the cathodal effects (26). Therefore it might be safer to use DC polarization in patients taking CBZ or other AEDs with a similar mechanism of action (i.e., sodium channel blocker).

Finally it should be noted that, although the patient with multifocal abnormalities that received active treatment did not worsen, on the contrary, improved electrophysiologically and clinically, this patient had an increase in the number of EDs in the area of the anode electrode. Although this might represent data variability, as only one patient with multifocal abnormalities received active treatment, it might be taken as a suggestion that positioning the anode electrode over an epileptogenic focus might indeed enhance EDs. Future studies should further investigate the effects of DC brain polarization in patients with multifocal lesions to clarify this issue.

The results of this study are in line with the results of other techniques of noninvasive and invasive brain stimulation, such as repetitive transcranial magnetic stimulation (rTMS) and subdural cortical stimulation. In rats, slow-frequency rTMS prolonged the latency for the development of pentylenetetrazol-induced seizures (3) and had an antikindling effect (27). In humans, low-frequency rTMS can reduce the number of seizures in patients with partial epilepsy (28) and epilepsy due to MCD lesions (4–6). Although a previous controlled study failed to find beneficial effects of rTMS on seizure control (29), it showed a trend toward a short-term decrease in seizures that was more pronounced in patients with neocortical foci. Finally, cortical stimulation using subdural electrodes decreases spike frequency in patients with neocortical epilepsy (30).

Despite the positive effects of these techniques of brain stimulation on seizure control, their mechanisms of action are still elusive. Repetitive brain stimulation has been extensively associated with an induction of long-term potentiation (LTP) and depression (LTD). Although the effects of DC polarization have also been associated with synaptic changes, this mechanism might be more appropriate to explain the effects of anodal stimulation. Indeed, in a recent well-conducted study, Priori et al. (2005) showed that cathodal stimulation changes not only the motor evoked potential, the motor threshold, and brain activity indexed by EEG, but also the excitability of low-threshold peripheral motor axons. Therefore the authors suggested that cathodal brain polarization would have an effect through nonsynaptic mechanisms and speculated that changes induced by cathodal DC polarization could be caused by modifications in transmembrane proteins and electrolysis-related changes in $H^+$ (31). Although speculative, another possible explanation is that cathodal stimulation weakens the efficacy of the *N*-methyl-D-aspartate (NMDA) receptors by neuronal activity diminution (decrease in the cortical excitability) and hyperpolarization of the postsynaptic membrane potential (32).

The electrophysiologic and clinical data of our study show a significant variance that can be explained by several factors such as medications and type of lesion, but one factor might, perhaps, be the most important to explain the variability of our data: the orientation of the neurons versus the orientation of the electric current. Several studies have shown that the effects of a constant electric field depend on the orientation of the excitable tissue in human cortex (33), cardiac ganglion of lobster (34), and cat cerebral cortex (35). This effect may be particularly important for our study, as it has been shown that cortical dysplasia is seen with a derangement of the cortical laminar structure and dysplastic changes in the neurons (36) that modify the orientation of these neurons. Therefore the effects of cathodal brain polarization may be less predictable in this population of patients compared with healthy controls. Another aspect is that because patients were taking CBZ (which inhibits the excitability-enhancing anodal effects), this may have resulted in a somewhat "pure" cathodal effect in the mixed oriented neurons. Future studies should evaluate the influence of MCD lesions in investigating different electrodes montages, and consequently, current orientation.

A few limitations of the present study should be mentioned. First, the sample size of this study was small, and therefore we could have incurred a type II error when reporting our results for the seizure frequency. However, the primary aim of the study was safety (i.e., this treatment would not provoke seizures), and the trend toward seizure reduction should be taken as encouraging for further studies. Second, the population of this study is not homogeneous regarding the size and depth of lesions. Although this inhomogeneity could bias the results, the randomization distributed patients with different types of lesions equally across the sham and active DC polarization groups. In addition, our findings were consistent across patients with different types of lesions.

In summary, the findings of our study suggest that cathodal DC polarization does not provoke seizures within hours of stimulation and is well tolerated in patients with refractory epilepsy and MCDs. Although several studies have shown that DC polarization can indeed modulate cortical activity noninvasively, only a few studies have investigated its clinical effect in neurologic patients; recent studies have demonstrated that this technique can improve motor function after stroke (37–39). Given that the results of our study show that this technique decreased the excitability in the epileptogenic focus and might reduce seizure frequency, these findings together encourage further studies to explore the clinical effects of this technique on epilepsy.

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