BRAIN INJURY
https://doi.org/10.1080/02699052.2017.1390254

High-Definition transcranial direct current stimulation in early onset epileptic encephalopathy: a case study

Oded Meiron[a], Rena Gale[b], Julia Namestnic[b], Odeya Bennet-Back[c], Jonathan David[a], Nigel Gebodh[d], Devin Adair[d], Zeinab Esmaeilpour[d,e], and Marom Bikson[d]

[a]Clinical Research Center for Brain Sciences, Herzog Medical Center, Jerusalem, Israel; [b]Children Respiratory Unit, Herzog Medical Center, Jerusalem, Israel; [c]Pediatric Neurology Department, Shaare Zedek Medical Center, Jerusalem, Israel; [d]Department of Biomedical Engineering, The City College of the City University of New York, New York, USA; [e]Biomedical Engineering Department, Amirkabir University of Technology, Tehran, Iran

ABSTRACT

Primary objective: Early onset epileptic encephalopathy is characterized by high daily seizure-frequency, multifocal epileptic discharges, severe psychomotor retardation, and death at infancy. Currently, there are no effective treatments to alleviate seizure frequency and high-voltage epileptic discharges in these catastrophic epilepsy cases. The current study examined the safety and feasibility of High-Definition transcranial direct current stimulation (HD-tDCS) in reducing epileptiform activity in a 30-month-old child suffering from early onset epileptic encephalopathy. Design and Methods: HD-tDCS was administered over 10 intervention days spanning two weeks including pre- and post-intervention video-EEG monitoring. Results: There were no serious adverse events or side effects related to the HD-tDCS intervention. Frequency of clinical seizures was not significantly reduced. However, interictal sharp wave amplitudes were significantly lower during the post-intervention period versus baseline. Vital signs and blood biochemistry remained stable throughout the entire study. Conclusions: These exploratory findings support the safety and feasibility of 4 × 1 HD-tDCS in early onset epileptic encephalopathy and provide the first evidence of HD-tDCS effects on paroxysmal EEG features in electroclinical cases under the age of 36 months. Extending HD-tDCS treatment may enhance electrographic findings and clinical effects.

ARTICLE HISTORY
Received 5 March 2017
Revised 3 October 2017
Accepted 5 October 2017

KEYWORDS
Seizure; video- EEG; interictal sharp waves; electroclinical syndrome; hypsarrhythmia

Introduction

Epileptic encephalopathy syndromes such as Ohtahara syndrome (OS), present during infancy (first 3 months), can invoke frequent continuous tonic spasms, focal motor seizures, hemiconvulsions, generalized tonic-clonic seizures, focal myoclonus, and suppression-burst pattern (SB), which can be detected with electroencephalography (EEG) (1). This severe electroclinical condition is often classified as "infantile spasms with hypsarrhythmia" related to non-metabolic structural brain abnormalities and hypsarrhythmic EEG features consisting of multifocal spikes, sharp wave activity, and high-voltage slow wave activity (2–5). The prognosis is generally poor since newborns with Ohtahara syndrome frequently die during infancy and survivors invariably manifest severe psychomotor impairments and remain in a persistent vegetative state (6).

Only a few clinical case-studies support the use of specific antiepileptic drugs to combat the persistent seizures (e.g., tonic spasms) in these severe electroclinical syndromes (1,6). Importantly, it has been suggested that clinical seizures might result from intermittent interference in descending brainstem pathways that control spinal reflex activity; seizure severity is correlated with changes in hypsarrhythmic EEG features that may indicate a disconnection between the cortex and subcortical structures (5,6). Based on age-dependent epileptic encephalopathy etiology and prognosis, significantly reducing the clinical seizures could have a beneficial impact on the infant's survival. It may also significantly alleviate autonomic disturbances (such as respiratory distress) and is likely to reduce progression of pathology (6,7).

Suppression of epileptiform discharges and seizure frequency by application of inhibitory non-invasive neuromodulation may alter disease progression and improve the clinical outcome in these "catastrophic epilepsy" conditions (8,9). Accordingly, transcranial direct current stimulation (tDCS) reduced epileptic discharge frequency in adults, with no serious adverse events (10). The cathode electrode is typically placed on the scalp over the epileptic focus with the intention to reduce excitability (11,12). The safety aspects of tDCS are supported by exhaustive testing across diverse clinical populations and healthy volunteers (13). Tolerability studies in adults have in turn supported judicious clinical trials in children; there are no reported serious adverse effects over 2,800 sessions across 500 subjects aged 6 to 18 years old (13). Often – though not exclusively – children receive moderately lower doses of electrical stimulation than adults (< 2 mA) as computational models suggest that decreased head size results in comparably smaller brain current density (14). In small clinical trials, tDCS reduced epileptic discharge frequency in

CONTACT Oded Meiron oded@herzoghospital.org Herzog Medical Center, 96 Givat Shaul Street, Jerusalem 91035.

children ages 6 to 15 years old (9,15,16). Five consecutive days of 2 mA of cathodal tDCS reduced seizure frequency in 4- to 9- year-old patients with LGS. In a case study, epileptic seizures in an 11-year-old girl were reduced by 50 percent after 2 mA of tDCS applied 5 times a week for two weeks with the cathodal electrode over the epileptic focus (9) . To our knowledge, tDCS has not previously been assessed in children under 36 months old, including in any children diagnosed with neonatal epileptic encephalopathy.

We hypothesized that tDCS applied with a cathode placed over the brain region exhibiting consistent hypsarrhythmic high-voltage features (e.g., robust excitatory changes in electrical discharges) would attenuate subsequent paroxysmal epileptiform activity and seizure frequency in children less than 36 months old. In the current case of a 30-month-old patient, in line with our investigational attempt to significantly reduce seizure-frequency, we suggested applying a cathodal electrode over areas of paroxysmal ictal-related EEG discharges repeatedly over a period of 10 days. Importantly, in order to increase the efficiency and specificity of our intended focal cathodal (inhibitory) stimulation we employed a 4x1-ring High-Definition tDCS montage (17), expected to: 1) produce maximum intensity (18) and neuromodulation (19) at paroxysmal hypsarhythmic target-areas, 2) achieve optimal focality (20), and 3) result in minimum relative intensity outside the target area. Recent findings support a HD-tDCS 4x1-Ring configuration as a technique for delivering focal cortical stimulation in a predictable and adjustable manner by utilizing advanced computational forward models (21). These models can integrate baseline EEG data (22), individual anatomical data (14,23), and head-size data (as applied in the current investigation) in order to predict the optimal parameters for accurate targeting of most pronounced pathological-hypsarhythmic cortical networks. Specifically, we tested the feasibility of HD-tDCS in reducing the pathological EEG activity as a post-intervention decline in the frequency of seizures; reduction in number and amplitude of interictal sharp-waves (3); and power-attenuation of hypsarhythmic fast-wave oscillations (24–30 Hz, 30–70 Hz). In order to support HD-tDCS safety in children suffering from neonatal epileptic encephalopathy less than three years of age, the clinical functional status of the child, vital signs, and biochemistry were assessed over the course of the study.

Materials and methods

Study overview

The study was conducted at Herzog Medical Center Jerusalem, Israel. Approval was obtained from the Israel Ministry of Health and from the institute's local institutional review board. The study was conducted in accordance with the Declaration of Helsinki, and written informed consent was obtained from the patient's parents.

In general, in order to localize the area of tDCS intervention, we recorded baseline video-EEG every day for 10 days prior to intervention. Based on baseline and ongoing video-EEG sessions during HD-tDCS intervention, we employed a intervention video-EEG to test for significant changes in paroxysmal pathological EEG features (4,24,25) such as interictal epileptiform discharges (e.g., sharp waves), paroxysmal fast-wave activity (20 to 30 Hz), and most importantly, the frequency of clinical seizures (e.g., tonic spasms, myoclonic seizures). We preselected hypsarrhythmic sharp waves as an outcome measure (e.g., peak amplitudes of sharp waves) since it has been suggested that hypsarrhythmic paroxysmal slow-wave activity is more closely related to the pathogenetic mechanisms than epileptiform discharges in age-dependent epileptic encephalopathy (5). Additionally, amplitudes of hypsarrhythmic sharp waves are associated with weaker cortical inhibition over the striatopallidal system.

Specifically, the baseline-monitoring period consisted of 120 minutes of daily video-EEG recordings (between 14:00 to 17:00), where epileptic discharge frequency and foci were monitored and quantified. Following the baseline period, verum open-label 4 × 1 HD-tDCS was administered for 20 minutes each day for 2 weeks (5-days per week), with each day having an increased current intensity (0.1–1.0 mA). This adaptive stimulation regime was adopted since the overall goal of the study was to attempt to treat seizure-related pathological EEG activity. Video-EEG data were acquired each day concurrently with HD-tDCS administration. On intervention days 1, 3, 5, 6, 8 and 10, post HD-tDCS session (immediately after the stimulation) video-EEG data were acquired (120 minute sessions, between 14:00 to 17:00). HD-tDCS stimulus intensity and locations were chosen based on baseline EEG monitoring and computational finite element model outcomes. Post HD-tDCS treatment effects were assessed by utilizing video-EEG data (120 minutes per day, between 14:00 to 17:00) from days, 3, 10, 17, 24, 31, and 41 after the last day (day 10) of intervention (Figure 1).

Across the entire study, seizure frequency (number of clinical seizures across 120 minutes) and type were monitored and noted by 2 clinical neurophysiologists, independently. All seizures and interictal patterns were interpreted by a pediatric neurologist (i.e., pediatric epileptologist) with extensive clinical experience in neonatal epileptic syndromes.

Case

The patient we intended to treat was a 30-months-old male, hospitalized in the Pediatric Chronic Respiratory Care Department (Herzog Medical Center, Jerusalem) since the age of two months. He was born after an uneventful, full term second pregnancy with birth weight of 3,160 g through a normal vaginal delivery, to heathy young parents with an older healthy child. The patient was discharged and re-hospitalized at the age of five days due to feeding problems. Upon admission, repeated seizures with bradycardic spells and oxygen desaturation episodes appeared. The infant was treated with Phenytoin and Phenobarbital with no apparent effect. On EEG examinations, a burst-suppression pattern was identified and Ohtahara Syndrome was suspected. The anticonvulsive treatment was changed, but the convulsions continued and were complicated by repeated aspirations, which required respiratory treatment. His routine antiepileptic medication

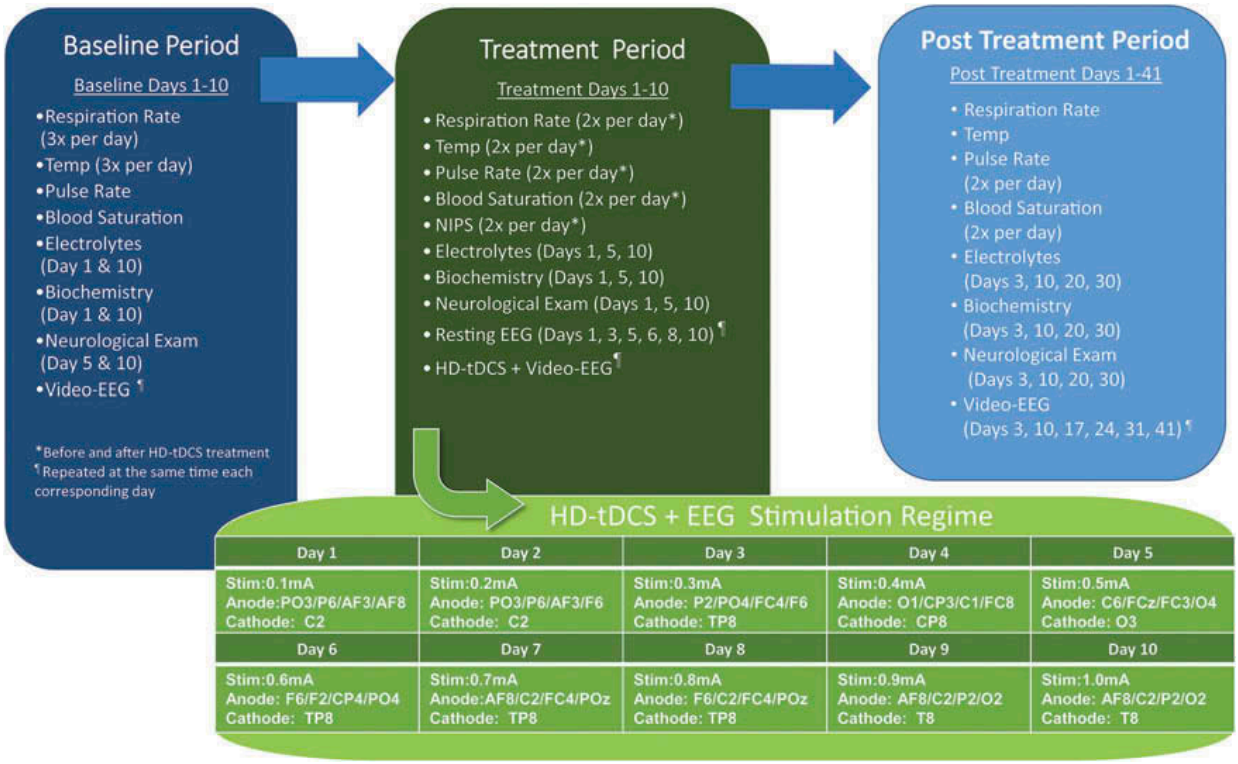

Figure 1. Study overview detailing assessments made during the baseline, intervention, and post- intervention periods. The HD-tDCS treatment consisted of a 10-day video-EEG and HD-tDCS stimulation protocol where stimulation intensities were increased from 0.1–1.0 mA over the course of the 10 days.

and Topiramate 100mg/day. An additional work-up included MRI scans, and amino acid levels in the blood and CSF, which were shown to be within normal limits (WNL). Urinary organic acid levels were also WNL and there were no positive findings on a skin biopsy. Electrolysis of transferrin had a slightly changed pattern. No dysmorphic features were found. The patient was chronically ventilated through a tracheostomy, and fed through a PEG. General hypotonicity was noticed with jerky movements and physical examination was WNL. He seemed to be in a vegetative state (i.e., unresponsive wakefulness), and demonstrated severe psychomotor retardation. At age two months, EEG during wakefulness revealed continuous non-synchronous tracing, including periods of SB, with frequent multifocal spikes. The clinical and electrographic patterns suggested neonatal epileptic encephalopathy, most consistent with early myoclonic epileptic encephalopathy (EMEE). However, age-dependent epileptic encephalopathy could not be excluded since differentiating between OS and EMEE can be difficult, and the two may represent different clinical manifestations of the same disease-continuum (6).

Neurological assessment and clinical monitoring

In order to support safety (and possibly efficacy) of HD-tDCS intervention, over the course of the study a pediatric neurologist, and the child's treating physicians, performed diagnoses and clinical assessments, respectively, at baseline, during HD-tDCS intervention, and for four weeks following the intervention; monitoring and noting the patient's clinical-functional status. Figure 1 illustrates the time line, including all neurological assessments and clinical data collection. Additionally, nursing team) at baseline and following all HD-tDCS intervention sessions using the behavioral pain scale (BPS) for critically ill patients (26).

Video-eeg acquisition and analysis

During this 10-day baseline monitoring period, video-EEG was acquired from a 32-channel electrode shielded cap (WaveGuard cap ANT-Neuro, The Netherlands) with an online 50 Hz notch filter, band-pass 0.16 – 100 Hz, sampling rate 512 Hz, averaged referenced, and amplified using an ANT 32 channel amplifier (ANT, Netherlands). The same EEG acquisition system was used for post-intervention period video-EEG acquisition and at particular days during the intervention period. During the baseline period, video-EEG was acquired every day for 10 days (between 14:00 to 17:00) prior to HD-tDCS intervention-period, in order to characterize the modified-hypsarhythmic paroxysmal EEG activity (2,3,5); the number and peak amplitudes of multi focal interictal spikes (e.g. sharp wave peak amplitudes), frequency of clinical seizures (visually analyzed using video-EEG), and the foci of modified hypsarhythmic ictal EEG discharges (marked using video-EEG, and seizure-related spectral analysis (noting spectral power differences between 3 sec pre-seizure time-window vs. 3 sec post-seizure time-window, with 0.25 sec offset) generating averaged spectral power head-maps of paroxysmal delta-band activity (5), ASA Netherlands) were collected and analyzed. Interictal discharges (e.g., number of sharp waves and their peak amplitudes) were quantified over 120 minutes of EEG data per day, using automated spike detection procedures (ASA ANT, Netherlands); counting all the sharp waves

and electrode location across all 32 electrodes. Seizures and interictal sharp-waves spikes were visually verified using video-EEG. Additionally, the raw EEG data (baseline versus post-intervention) was used for the spectral analysis (across all 32 channels with averaged reference) of the first 50 minutes of 120 minutes of EEG recordings, segmented to one-second epochs that were fast Fourier transformed (FFT) and averaged (and normalized) to produce the mean absolute power in delta (0.5–3.5 Hz), high beta-band (24–30 Hz) and gamma band (30–70 Hz) per EEG session. We employed the FFT analysis on all 32 electrodes since were interested to evaluate the topography of spontaneously fluctuating paroxysmal EEG delta power (5) in relevance to epileptic foci dominance. We used SPSS 20 software (IBM, Armonk, NY) for all statistical analyses related to seizure frequency, frequency of sharp waves sharp-wave peak-amplitudes, and spectral power at baseline period versus intervention/post-intervention periods.

Video-EEG data were also acquired concurrently with the HD-tDCS intervention (see Figure 2 depicting patient with hybrid EEG-HD-tDCS cap). These data were acquired from a customized 32-channel electrode montage based on the 10–20 International system (WaveGuard cap and eego amplifier ANT-Neuro, The Netherlands). The cap consisted of a combination of 32-recording electrodes as well as 29- plastic, integrated, HD electrode holders. The data sets were sampled between 512–2000 Hz and online referenced to electrode location CPz.

Concurrent EEG and HD-tDCS data were analyzed offline by performing a baseline correction between 0.5 and 30 secs after the start of data acquisition and applying a second order Butterworth band-pass filter between 0.5 and 45 Hz. During some concurrent EEG and HD-tDCS recordings, EEG electrodes were removed in order to insert stimulating electrodes. These absent electrodes were interpolated offline using a spherical interpolation method. During HD-tDCS intervention, several EEG electrodes became saturated; these specific electrodes were identified offline by computing the standard deviation of each electrode during a 31.25-second period after ramp-up was complete. Voltages that had a standard deviation less than 0.005 μV during the 31.25-second HD-tDCS period were marked as saturated. A linear least squared fit was performed on each electrode during the current ramp-up period to ameliorate data quality during the stimulation period. The slopes from the least squared fit were used to predict the DC voltage of the saturated electrodes (28.13% of electrodes) at the end of the ramp-up period. Scalp voltage topographies were computed by averaging a period 5.86 seconds after the current ramp-up period was completed. All concurrent EEG and HD-tDCS data analysis was performed using MATLAB (R2015b; MathWorks, Natick, MA) in concert with raw data-reading, channel interpolation and topographic plot functions from EEGLAB toolbox (27).

Hd-tdcs computational finite element model

Prior to the commencement of the study, a high resolution head model was generated based on an MRI of an age matched infant with $0.5mm^3$ resolution in order to predict current flow patterns. Specifically, we used a computational finite element model (FEM) of the head to predict the spatial distribution of electric fields in cortex and the voltage distribution over the skin for safety considerations and stimulation efficacy. Automated segmentation was first performed using SPM in order to segment images into six different tissues with conductivities assigned to each: skin (0.465 S/m), skull (0.01 S/m), air (1×10^{-15} S/m), CSF (1.65 S/m), grey matter (0.276 S/m), white matter (0.126 S/m), electrode (5.8×10^{7} S/m), and gel (1.4 S/m). Residual segmentation errors were corrected in ScanIP (Simpleware, Ltd., Exeter, UK) using a combination of segmentation tools. The resulting volumetric meshes were imported into a FEM solver (COMSOL, Burlington, MA, USA) for FE computation. 1 mA total current was applied at the center cathode electrodes. The 4 anodes received either symmetric 0.25 mA (Figure 3.E) or an asymmetric distribution (Figure 3.F) to match the experimental scalp DC potentials.

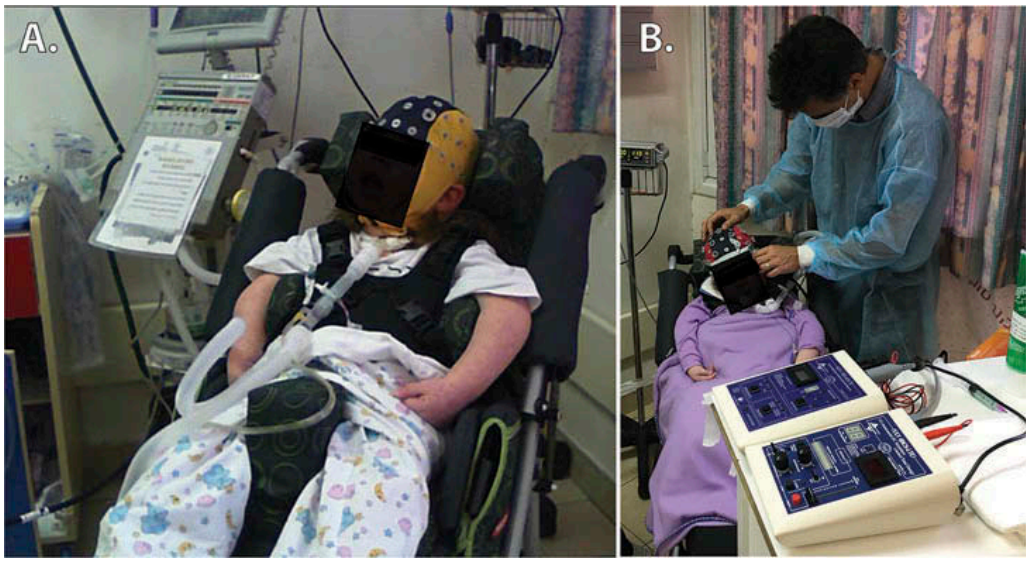

Figure 2. Patient photographs during HD-tDCS/video-EEG sessions. A) EEG cap placement and video-EEG set up with patient. B) Set up of HD-tDCS with concurrent

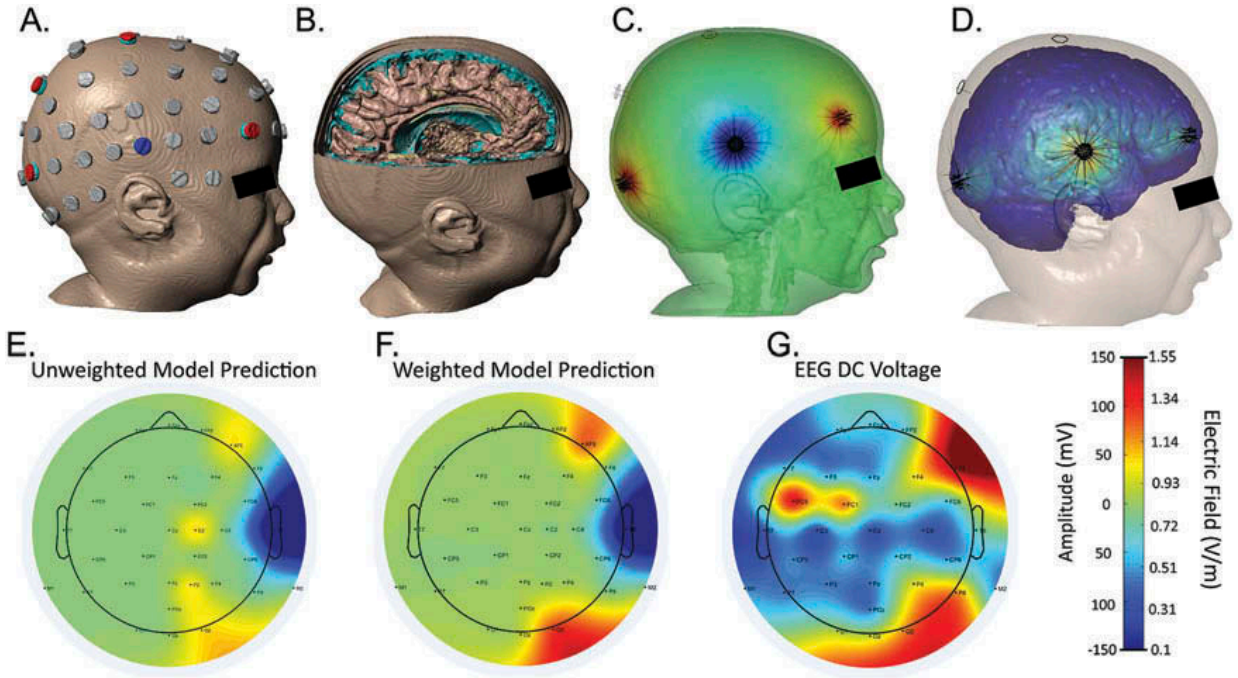

Figure 3. Age-matched head models before and during HD-tDCS. A) FEM MRI-derived model of an age-matched infant. The day 9–10 montage is shown where electrode positioning is based on the 10/10 International system. Locations were used for recording EEG (grey) and stimulation (blue: cathode; red: anode). B) FEM MRI-derived head model indicating skull and skin thickness, gray matter (pink), and cerebrospinal fluid (blue). C) Model-based prediction from FEM indicating current flow patterns (black flux lines) along with expected scalp voltages across the head and at the anodes and cathode. D) Model-based current flow patterns (black flux lines) and electric field across the brain. E) Model prediction of scalp topography during HD-tDCS. F) Weighted model prediction of scalp topography during HD-tDCS. The weighted model unevenly distributed current across the 4 anodes. The stimulating sites AF8 and O2 received 90% of current whereas stimulating sites C2 and P2 received the remaining 10% of current. G) Scalp topography averaged over 5.86 sec period during HD-tDCS showing the DC voltage.

Hd-tdcs intervention

HD-tDCS treatment intervention was applied according to the 4 × 1 montage (17) with a center cathode using a Soterix Medical 1 × 1 LTE [extra voltage limited (28),] stimulator and 4 × 1 HD-tDCS montage adaptor (29,30). The cathode was positioned over seizure related dominant areas (e.g. right temporal) and the four anode electrodes were positioned around it in the 4 × 1 ring configuration (see Figure 3A). Stimulation was administered repeatedly, over a period of 10 days (20 minutes per day, current range of 0.1 mA to 1 mA, 5 times a week for 2 weeks starting between 12:00–13:00). Since this was an exploratory and a novel treatment application in a young child and since safety was paramount, stimulation commenced with an extremely low current intensity (0.1 mA on the first day) and gradually increased (raised in increments of 0.1 mA per day) to a maximum of 1 mA on the last treatment session. Additionally, since neonatal epileptic encephalopathy cases are characterized by multifocal spikes and seizure intractability we monitored seizure-related delta power changes and paroxysmal interictal spike topography every day, and modified the HD-tDCS montage accordingly. Although it is a non-consistent location/dosage methodology, it fits well with our aim-to-treat primary research goal; as our main objective is to establish safety and a significant clinical impact using HD-tDCS (to the best of our knowledge for the first time) in "catastrophic epilepsies" (under the age of 36 months) associated with persistent mental deterioration accompanied with the preservation of seizures throughout their entire life. Furthermore, 50% of neonatal epileptic encephalopathy syndrome cases often die before two years of age, which leaves a very narrow time-window for treatment interventions (1,6).

The general montage features (e.g. distance between center and ring electrodes) were designed using high-resolution computational models. As recent MRI scans of the patient were not available, and the condition of the patient made imaging risky, we developed a model based on an age and head-size matched subject scan (See section on Computational Finite Element Model) using an established workflow (17,18,31).

Results

Selected hd-tdcs montages for intervention period

Intervention Day 1: Based on the last three days of the baseline EEG recordings (22), we identified a target electrode-location for the placement of the center-cathode electrode over the right motor cortex area electrode C2. This first target-montage for treatment was based on observing maximal interictal slow-spike wave amplitudes, sharp waves, and maximal ictal-related paroxysmal delta absolute power changes over an area spanning across FC2, P8, and CP6 electrodes on the three days that preceded intervention onset. Electrode C2 was chosen as the first target electrode-location, representing a topographical point in between electrodes showing maximal paroxysmal electroclinical activity. Intervention Days 2–5: Daily video-EEG monitoring after each intervention suggested a shift in the location of the paroxysmal seizure-related activity, resulting in a different placement of the center cathode towards right lateral temporal or right parietal or left occipital target location. Intervention Days 6–10: During the second week, we maintained the same HD-tDCS montage for days 6, 7 and 8

positioning the central cathode over the right lateral temporal-parietal electrode TP8 and on days 9 and 10 over lateral temporal electrode T8. Overall, 90% of the HD-tDCS montages used were applied over the right hemisphere (frontal-parietal and temporal-parietal cortices).

Safety and clinical findings

Pulse rate during baseline (mean = 107 bpm, SD = ± 17.16 bpm) was normal and remained within normal limits during intervention (mean = 103.35 bpm, SD = ± 18.78 bpm) and post intervention (mean = 92.5 bpm, SD = ± 15.47 bpm) periods. There were no significant fluctuations in respiratory rate (20–23 breaths per minute), temperature (35.1–37.2°C), or blood saturation (98%-100% SpO2) throughout the entire study period. Accordingly, the intervention was considered safe and had no negative impact on the patient's vital signs, electrolyte levels or blood biochemistry. Importantly, no adverse events or side effects were observed during the study period. The skin under the stimulating electrodes was not irritated and the patient did not display any changes in behavior associated with pain [e.g., facial expressions, movement of arms, berating patterns; 31] during or following the HD-tDCS sessions.

Neurological findings

At the initial neurologic examination – prior to intervention – we found that the child did not achieve any developmental milestones. He was bedridden. His spontaneous movements were very limited and rare. He was ventilated permanently and fed through PEG. He responded to pain stimulation by opening his eyes or moving a limb. He did not respond to touch, visual or auditory stimulation. He was not making any eye contact. He had severe axial hypotonia with increased spastic muscle tone at distal lower limbs. Range of joints motion was limited at the hamstrings and Achilles bilaterally. Deep tendon reflexes were not elicited. There was no clonus and plantar response was not elicited (not flexor nor extensor response bilaterally). Corneal reflex was elicited at the left but not on the right eye, and pharyngeal reflexes existed but were very weak. Pupils were narrow without response to light. On subsequent examinations during the intervention period there were minor changes in the neurological examination: the plantar response was elicited and was bilaterally extensor; and corneal reflexes were elicited bilaterally. Neurological findings during post-intervention remained the same. Overall there was no significant change on neurological examinations and development throughout the study.

Video-eeg

A one sample Kolmogorov Smirnov test indicated that the variable values of frequency of seizures (number of seizures per 120 mins video-EEG sessions) were distributed normally within the baseline (Z = 0.63, p = 0.82), and post-intervention (Z = 0.9, p = 0.38) periods. A paired samples t test indicated that baseline seizure frequency (M = 198, SD = 49.65) was not significantly different ($t(4)$ = −0.61, p = 0.57) from post-intervention seizure frequency (M = 236, SD = 130.17). The intervention period versus baseline period was not significantly different in seizure frequency ($t(4)$ = −2.63, p = .058). A non-significant reduction ($t(5)$ = .98, p = 0.36) in the number of sharp waves was observed at post-intervention period versus baseline period (see Figure 4.A). Kolmogorov Smirnov tests indicated that the peak amplitudes of sharp waves during the baseline and post-intervention periods were not distributed normally. Thus we performed a nonparametric related samples test (Friedman's two-way ANOVA) to examine significant differences between baseline and post-intervention periods in the peak amplitudes of hypsarrhythmic interictal sharp waves. We compared the last three days of baseline (days 8, 9, and 10) to the first three post-intervention measurements (3, 10 and 17 days intervention) and found that

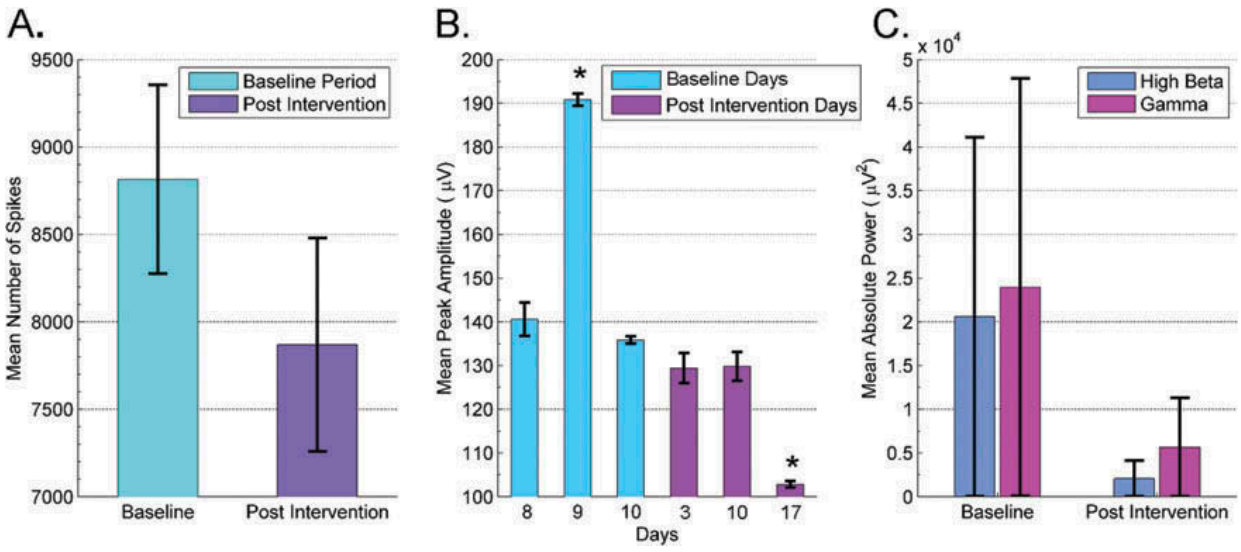

Figure 4. Epileptiform interictal activity of baseline period versus post-intervention period. A) The number of sharp waves was compared at post-intervention versus baseline. B) The last three days of baseline (days 8, 9, and 10) were compared with the first three post-intervention measurements (3, 10 and 17 days post last day of intervention). It was found that sharp wave peak amplitudes were significantly different (Friedman's two way analysis of variance by ranks test, p < .001) and lower at day 17 post-intervention (rank = 2.93) versus all other days. C) Inspection of the spectral power data as a function of time suggests a trend indicating lower power

sharp wave peak amplitudes were significantly different ($p < .001$) and lower at day 17 post-intervention (rank = 2.93) versus all other days (see post-intervention day 17 mean peak amplitudes in Figure 4.B), where baseline day 9 had the highest rank (4.39). Pairwise comparisons indicated that only post-intervention-days one and three were not significantly different from each other, all the other days were significantly different from each other ($p < .01$ for two comparisons, and $p < .001$ for all other comparisons).To correct for multiple comparisons we conducted post-hoc analysis with Wilcoxon signed-rank test to examine the difference between baseline day 9 and three post-intervention days. According the post-hoc analysis baseline day 9 showed significantly higher peak sharp-wave amplitudes than post-intervention day 17 ($Z = -54.16$, $p < .0001$), post-intervention day 10 ($Z = -31.48$, $p < .001$), and post-intervention day 3 ($Z = -35.9$, $p < .001$).In correspondence, post-hoc Wilcoxon signed-rank test indicated that post-intervention day 17 showed significantly lower spike amplitudes than baseline day 8 ($Z = -20.7$ $p < .001$), and baseline day 10 ($Z = -32.22$, $p < .001$). In order to compare the immediate HD-tDCS effects on sharp wave peak-amplitudes as a function of intervention day we conducted a Wilcoxon signed-rank test comparing intervention days 3, 6, 8, and 10 to baseline day 10. Interestingly, in contrast to post-intervention reduction in spike-amplitudes, all intervention days showed significantly higher ($p < .001$) sharp wave amplitudes immediately following stimulation versus baseline day 10 sharp wave peak amplitudes. The highest Z scores were obtained for intervention day 3 ($Z = -21.84$) and intervention day 8 ($Z = -36.73$). Thus, 0.3 mA with central-cathode over right parietal location (intervention day 3) and 0.8 mA with central cathode over right temporal-parietal location (intervention day 8 showed the greatest impact versus Intervention day 6 (0.6 mA with cathode at right temporal-parietal location) and 10 (1 mA with right temporal location).The obtained differences in immediate sharp wave amplitudes seems to imply that targeting right temporal-parietal foci may have had a greater impact on the underlying electrophysiological activity, starting with relatively low 0.3 mA current dosage. Finally, we examined differences in the averaged absolute power of fast-wave oscillations in the baseline period versus post intervention period. Kolmogorov Smirnov test indicated that the high-beta (24–30 Hz) and gamma (30–70 Hz) band's absolute power values within each EEG session were normally distributed. The high-beta and gamma mean absolute power at baseline was not significantly different from post-intervention, ($t(5) = 0.88$, $p = .41$) and ($t(5) = 0.71$, $p = .5$), respectively. Although the effect of time was non-significant, inspection of the spectral power data as a function of time indicated lower power values at post-stimulation (See Figure 4.C). In response to recent findings suggesting that paroxysmal fast-wave activity (independent of sharp wave activity) is likely to precede or follow ictal slow waves in cases of neonatal epileptic encephalopathy (4), we found a significant correlation (Spearman's rho = .49, $p = .04$) between paroxysmal high-beta power and the number of interictal sharp waves throughout the clinical trial.

Discussion

This was an open-label aim-to-treat case study of repeated HD-tDCS sessions to reduce seizure frequency and pathological EEG activity in a child suffering from early onset epileptic encephalopathy. To apply focal inhibitory stimulation at the cathodal electrode and minimize excitation at the anode (s), we used a 4 × 1 HD-tDCS montage (17,23) which was customized to the child using modeling from an age-matched control. tDCS, with intensities up to 2 mA is considered well tolerated in children (13,32). The electric fields (EF) predicted in the child's brain at 1 mA (the highest current tested in this study) was moderately higher (2-3x) than EF expected in adults and older children using comparable current, but still well below theoretical thresholds for injury (13). Tolerability, which is related to transient skin irritation, depends on electrode design and total current (13), which were comparable to tDCS montages and currents used in prior studies (33).

By virtue of using a DC waveform as an intervention for epileptic disorders, "cathodal" tDCS is the only neuromodulation technique that can produce a sustained somatic membrane hyperpolarization (34); which in turn has been shown to have a robust anti-seizure effect in animal models (12,35). Cathodal tDCS also leads to a lasting reduction in cortical excitability in healthy volunteers (19). These findings have supported ongoing human trials for epilepsy (36). The majority of these efforts use a conventional tDCS montage with two large pads electrodes, an anode and cathode, with the cathode placed over the target brain region to produce neural hyperpolarization. But with this approach the anode remains active, producing secondary excitation, and consequently other brain regions between the electrodes will be stimulated resulting in diffuse neuromodulation (17,37). Our use of the 4 × 1 HD-tDCS montage was based on prior work that suggested focal and uni-directional action (21). The cortical region circumscribed by the ring (from the center cathode to the four outer electrodes) is the predicted region of neural hyperpolarization (18) that was adjusted based on time-dependent (daily) focal pathological EEG discharges using the model-free method (22).

There were no serious adverse events or side effects associated with the intervention as evidenced by the stable level of vital signs, electrolytes levels, and blood biochemistry. Additionally, the neurological assessments indicated that the overall clinical and developmental status remained the same. In clinical populations there is a need to maintain normal vigilance (e.g. an unrelated emergency); based on this pilot study, we did not find evidence for increased risk as result of the intervention. Furthermore, according to his treating physicians, the clinical impression following HD-tDCS intervention indicated that the patient is apparently calmer and displays lower-intensity seizures, which is likely to result in less comorbid medical complications (e.g., bradycardic spells and oxygen desaturation). Therefore, our findings support the safety of HD-tDCS intervention in severe electroclinical syndrome cases under the age of three years.

Although we did not observe a significant reduction in the frequency of seizures in the periods during which video-EEG was collected, we obtained a significant reduction in the peak-amplitudes of hypsarrhythmic interictal sharp waves. Therefore, this finding could be viewed as a significant reduction in interictal epileptiform discharges (IED). In support of this, significant reduction in IED components are associated with significant improvement in 74–92% of temporal lobe epilepsy patients and diffuse temporal IEDs occur in more than 50% of the patients (38). Although we did not achieve a significant improvement in the seizure frequency or the overall clinical condition of the child, we hypothesize that application of 1mA HD-tDCS (the highest dose, tested only on day 10) over an extended period may yield the desired alleviation in seizure frequency. Additionally, sampling seizure frequency and sharp-wave variables from more time-windows within the baseline and post-intervention periods (as opposed to sampling only from five or six days per period in the current study) may have resulted in an observable significant effect versus the non-significant reduction observed in seizure frequency, as well as in sharp wave frequency and paroxysmal fast-wave activity.

As this HD-tDCS intervention is considered a novel treatment approach in a child under the age of 36 months – for safety reasons – we applied very low current intensities in the first week, which most likely had a nonsignificant long-term inhibitory impact on the underlying neural substrate and on paroxysmal IEDs. Since IEDs are likely to occur after seizures, and are correlated with higher seizure frequency (38), it might be beneficial to continue with longer HD-tDCS interventions, with the highest tested safe dosage, until we reach a greater reduction in additional IED components (e.g., number of sharp waves), which is hypothesized to result in a more pronounced reduction in the occurrences of clinical seizures. Additionally, it may have been more clinically beneficial to begin intervention at an earlier age (1 to 6 months of age) as we may have been more successful in modifying the initial pathological progression (associated with age-specific exogenous brain insult) of the epileptic foci dominance and possibly change the evolution of this severe electroclinical syndrome (1).

Generalized paroxysmal fast activity (such as high beta and gamma frequencies), is among the most indicative paroxysmal EEG features in infantile spasms with hypsarrhythmia (24,39). Interestingly, the significant correlation found between high-beta power and the number of sharp-wave spikes supports the utilization of paroxysmal high-beta analyses in the identification of paroxysmal EEG features (24) and epileptiform activity (4).

Conclusions

For young children and infants suffering from catastrophic epilepsies there is an urgent need to develop and test new interventions to suppress seizure activity, which is often resistant to anti-epileptic medication and conventional therapies (1,6). Without such relief, co-morbid complications sacrifice quality of life, retard neurological and physical development, present a high burden of care, and can lead to early mortality. Given this expected poor prognosis, considered safe in healthy volunteers and encouraging data from ongoing tDCS trials in various (pediatric) epilepsy indications, putatively support the safety of HD-tDCS application in very young catastrophic epilepsy cases, and ongoing testing of the potential of tDCS treatment for severe neonatal epileptic conditions. To fully support the safety, and assess the potential efficacy of HD-tDCS treatment in severe neonatal epileptic syndromes it would be imperative to validate its effects on pathological EEG activity and clinical seizures in larger samples of children under 36 moths.

Disclosure statement

The City University of New York has patent on brain stimulation with Marom Bikson as inventor. MB has equity in Sotetix Medical Inc which makes brain stimulation devices. The authors declare no sources of funding for the current study.

References

1. Ohtahara S, Yamatogi Y. Ohtahara syndrome: with special reference to its developmental aspects for differentiating from early myoclonic encephalopathy. Epilepsy Res. 2006;70:58–67. doi:10.1016/j.eplepsyres.2005.11.021.
2. Hrachovy RA, Frost JD, Kellaway P. Hypsarrhythmia: variations on the theme. Epilepsia. 1984;25(3):317–25. doi:10.1111/epi.1984.25.issue-3.
3. Watanabe K, Negoro T, Aso K, Matsumoto A. Reappraisal of interictal electroencephalograms in infantile spasms. Epilepsia. 1993;34(4):679–85. doi:10.1111/epi.1993.34.issue-4.
4. Gaily E, Liukkonen E, Paetau R, Rekola M, Granström ML. Infantile spasms: diagnosis and assessment of treatment response by video-EEG. Dev Med Neurol. 2001;43(10):658–67. doi:10.1017/S0012162201001207.
5. Siniatchkin M, Van Baalen A, Jacobs J, Moeller F, Moehring J, Boor R, Wolff S, Jansen O, Stephani U. Different neuronal networks are associated with spikes and slow activity in hypsarrhythmia. Epilepsia. 2007;48(12):2312–21.
6. Beal JC, Cherian K, Moshe SL. Early-onset epileptic encephalopathies: ohtahara syndrome and early myoclonic encephalopathy. Pediatr Neurol. 2012;47(5):317–23. doi:10.1016/j.pediatrneurol.2012.06.002.
7. Yamamoto H, Okumura A, Fukuda M. Epilepsies and epileptic syndromes starting in the neonatal period. Brain Dev. 2011;33(3):213–20. doi:10.1016/j.braindev.2010.10.009.
8. Sunderam S, Gluckman B, Reato D, Bikson M. Toward rational design of electrical stimulation strategies for epilepsy control. E&B. 2010;17(1):6–22. Epub 2009/ 11/21. doi:10.1016/j.yebeh.2009.10.017. PubMed PMID: 19926525; PubMed Central PMCID: PMCPMC2818293.
9. Yook S-W, Park S-H, Seo J-H, Kim S-J, Ko M-H. Suppression of seizure by cathodal transcranial direct current stimulation in an epileptic patient-a case report. Ann Rehabil Med. 2011;35(4):579–82. doi:10.5535/arm.2011.35.4.579.
10. Fregni F, Thome-Souza S, Nitsche MA, Freedman SD, Valente KD, Pascual-Leone A. A controlled clinical trial of cathodal DC polarization in patients with refractory epilepsy. Epilepsia. 2006;47(2):335–42. doi:10.1111/epi.2006.47.issue-2.
11. Brunoni AR, Nitsche MA, Bolognini N, Bikson M, Wagner T, Merabet L, Edwards DJ, Valero-Cabre A, Rotenberg A, Pascual-Leone A, et al. Clinical research with transcranial direct current stimulation (tDCS): challenges and future directions. Brain Stimul. 2012;5(3):175–95. doi:10.1016/j.brs.2011.03.002.
12. Ghai RS, Bikson M, Durand DM. Effects of applied electric fields on low-calcium epileptiform activity in the CA1 region of rat

13. Bikson M, Grossman P, Thomas C, Zannou AL, Jiang J, Adnan T, Mourdoukoutas AP, Kronberg G, Truong D, Boggio P, et al. Safety of transcranial direct current stimulation: evidence based update 2016. Brain Stimul. 2016;9(5):641–61. doi:10.1016/j.brs.2016.06.004.
14. Kessler SK, Minhas P, Woods AJ, Rosen A, Gorman C, Bikson M. Dosage considerations for transcranial direct current stimulation in children: a computational modeling study. PLoS One. 2013;8(9):e76112. doi:10.1371/journal.pone.0076112.
15. Auvichayapat N, Rotenberg A, Gersner R, Ngodklang S, Tiamkao S, Tassaneeyakul W, Auvichayapat P. Transcranial direct current stimulation for treatment of refractory childhood focal epilepsy. Brain Stimul. 2013;6(4):696–700. doi:10.1016/j.brs.2013.01.009.
16. Auvichayapat N, Sinsupan K, Tunkamnerdthai O, Auvichayapat P. Transcranial direct current stimulation for treatment of childhood pharmacoresistant lennox-gastaut syndrome: a pilot study. Front Neurol. 2016;7:16.
17. Datta A, Bansal V, Diaz J, Patel J, Reato D, Bikson M. Gyri-precise head model of transcranial direct current stimulation: improved spatial focality using a ring electrode versus conventional rectangular pad. Brain Stimul. 2009;2(4):201–7.e1. doi:10.1016/j.brs.2009.03.005.
18. Alam M, Truong DQ, Khadka N, Bikson M. Spatial and polarity precision of concentric high-definition transcranial direct current stimulation (HD-tDCS). Phys Med Biol. 2016;61(12):4506–21. doi:10.1088/0031-9155/61/12/4506.
19. Kuo H-I, Bikson M, Datta A, Minhas P, Paulus W, Kuo M-F, Nitsche MA. Comparing cortical plasticity induced by conventional and high-definition 4 × 1 ring tDCS: a neurophysiological study. Brain Stimul. 2013;6(4):644–48. doi:10.1016/j.brs.2012.09.010.
20. Dmochowski JP, Datta A, Bikson M, Su Y, Parra LC. Optimized multi-electrode stimulation increases focality and intensity at target. J Neural Eng. 2011;8(4):046011. doi:10.1088/1741-2560/8/4/046011.
21. Edwards D, Cortes M, Datta A, Minhas P, Wassermann EM, Bikson M. Physiological and modeling evidence for focal transcranial electrical brain stimulation in humans: a basis for high-definition tDCS. Neuroimage. 2013;74:266–75. doi:10.1016/j.neuroimage.2013.01.042.
22. Cancelli A, Cottone C, Tecchio F, Truong DQ, Dmochowski J, Bikson M. A simple method for EEG guided transcranial electrical stimulation without models. J Neural Eng. 2016;13(3):036022. doi:10.1088/1741-2560/13/3/036022.
23. Gillick BT, Kirton A, Carmel JB, Minhas P, Bikson M. Pediatric stroke and transcranial direct current stimulation: methods for rational individualized dose optimization. Front Hum Neurosci. 2014;8:739.
24. Wong-Kisiel LC, Nickels K. Electroencephalogram of age-dependent epileptic encephalopathies in infancy and early childhood. Epilepsy Res Treat. 2013;2013:18. doi:10.1155/2013/743203.
25. Weckhuysen S, Mandelstam S, Suls A, Audenaert D, Deconinck T, Claes LR, Deprez L, Smets K, Hristova D, Yordanova I, et al. KCNQ2 encephalopathy: emerging phenotype of a neonatal epileptic encephalopathy. Ann Neurol. 2012;71(1):15–25. doi:10.1002/ana.22644.
26. Payen J-F, Bru O, Bosson J-L, Lagrasta A, Novel E, Deschaux I, Lavagne P, Jacquot C. Assessing pain in critically ill sedated patients by using a behavioral pain scale. Crit Care Med. 2001;29(12):2258–63. doi:10.1097/00003246-200112000-00004.
27. Delorme A, Makeig S. EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. J Neurosci Methods. 2004;134(1):9–21. doi:10.1016/j.jneumeth.2003.10.009.
28. Hahn C, Rice J, Macuff S, Minhas P, Rahman A, Bikson M. Methods for extra-low voltage transcranial direct current stimulation: current and time dependent impedance decreases. Clin Neurophysiol. 2013;124(3):551–556.
29. Caparelli-Daquer EM, Zimmermann TJ, Mooshagian E, Parra LC, Rice JK, Datta A, Bikson M, Wassermann EM. A pilot study on effects of 4 × 1 high-definition tDCS on motor cortex excitability. Annu Int Conf IEEE Eng Med Biol Soc IEEE Eng Med Biol Soc Annu Conf. 2012;2012:735–38.
30. Villamar MF, Wivatvongvana P, Patumanond J, Bikson M, Truong DQ, Datta A, Fregni F. Focal modulation of the primary motor cortex in fibromyalgia using 4x1-ring high-definition transcranial direct current stimulation (HD-tDCS): immediate and delayed analgesic effects of cathodal and anodal stimulation. J Pain. 2013;14(4):371–83. doi:10.1016/j.jpain.2012.12.007.
31. Minhas P, Bikson M, Woods AJ, Rosen AR, Kessler SK. Transcranial direct current stimulation in pediatric brain: a computational modeling study. Annu Int Conf IEEE Eng Med Biol Soc IEEE Eng Med Biol Soc Annu Conf. 2012;2012:859–62.
32. Gillick BT, Feyma T, Menk J, Usset M, Vaith A, Wood TJ, Worthington R, Krach LE. Safety and feasibility of transcranial direct current stimulation in pediatric hemiparesis: randomized controlled preliminary study. Phys Ther. 2015;95(3):337–49. doi:10.2522/ptj.20130565.
33. Nitsche MA, Cohen LG, Wassermann EM, Priori A, Lang N, Antal A, Paulus W, Hummel F, Boggio PS, Fregni F, et al. Transcranial direct current stimulation: state of the art 2008. Brain Stimul. 2008;1(3):206–23. doi:10.1016/j.brs.2008.06.004.
34. Bikson M, Inoue M, Akiyama H, Deans JK, Fox JE, Miyakawa H, Jefferys JGR. Effects of uniform extracellular DC electric fields on excitability in rat hippocampal slices in vitro. J Physiol. 2004;557(Pt 1):175–90. doi:10.1113/jphysiol.2003.055772.
35. Liebetanz D, Klinker F, Hering D, Koch R, Nitsche MA, Potschka H, Löscher W, Paulus W, Tergau F. Anticonvulsant effects of transcranial direct-current stimulation (tDCS) in the rat cortical ramp model of focal epilepsy. Epilepsia. 2006;47(7):1216–24. doi:10.1111/j.1528-1167.2006.00539.x.
36. Gschwind M, Seeck M. Transcranial direct-current stimulation as treatment in epilepsy. Expert Rev Neurother. 2016;16:1–15.
37. Bikson M, Datta A, Rahman A, Scaturro J. Electrode montages for tDCS and weak transcranial electrical stimulation: role of "return" electrode's position and size. Clin Neurophysiol. 2010;121(12):1976–78. doi:10.1016/j.clinph.2010.05.020.
38. Pillai J, Sperling MR. Interictal EEG and the diagnosis of epilepsy. Epilepsia. 2006;47(s1):14–22. doi:10.1111/epi.2006.47.issue-s1.
39. Arzimanoglou A, French J, Blume WT, Cross JH, Ernst J-P, Feucht M, Genton P, Guerrini R, Kluger G, Pellock JM, et al. Lennox-Gastaut syndrome: a consensus approach on diagnosis, assessment, management, and trial methodology. Lancet Neurol. 2009;8(1):82–93. doi:10.1016/S1474-4422(08)70292-8.