Original article

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Transcranial direct current stimulation improves seizure control in patients with Rasmussen encephalitis

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ABSTRACT – *Aim*. Rasmussen encephalitis is associated with severe seizures that are unresponsive to antiepileptic drugs, as well as immunosuppressants. Transcranial direct current stimulation (t-DCS) is a non-invasive and safe method tried mostly for focal epilepsies with different aetiologies. To date, there is only one published study with two case reports describing the effect of t-DCS in Rasmussen encephalitis. Our aim was to investigate the effect of t-DCS on seizures in Rasmussen encephalitis and to clarify its safety.

Methods. Five patients (mean age: 19; three females), diagnosed with Rasmussen encephalitis were included in this study. Patients received first cathodal, then anodal (2 mA for 30 minutes on three consecutive days for non-sham stimulations), and finally sham stimulation with two-month intervals, respectively. Three patients received classic (DC) cathodal t-DCS whereas two patients received cathodal stimulation with amplitude modulation at 12 Hz. Afterwards, all patients received anodal stimulation with amplitude modulation at 12 Hz. In the last part of the trial, sham stimulation (a 60-second stimulation with gradually decreasing amplitude to zero in the last 15 seconds) was applied to three patients. Maximum current density was 571 mA/m2 using 70 mm x 50 mm wet sponge electrodes with 2-mA maximum, current controlled stimulator, and maximum charge density was 1028 C/m2 for a 30-minute stimulation period.

Results. After cathodal stimulation, all but one patient had a greater than 50% decrease in seizure frequency. Two patients who received modulated cathodal t-DCS had better results. The longest positive effect lasted for one

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month. A second trial with modulated anodal stimulation and a third with sham stimulation were not effective. No adverse effect was reported with all types of stimulations.
Conclusions. Both classic and modulated cathodal t-DCS may be suitable alternative methods for improving seizure outcome in Rasmussen encephalitis patients.

Key words: direct current stimulation, Rasmussen encephalitis, epilepsy

Rasmussen encephalitis (RE) is characterized by progressive deterioration related to one hemisphere resulting in hemiparesis, cognitive decline, and intractable unilateral focal motor seizures or secondary generalized seizures with onset mostly in childhood (Rasmussen *et al.,* 1958; Oguni *et al.,* 1991). RE can be bilateral only very rarely (Peariso *et al.,* 2013). Its diagnosis can be made according to the consensus criteria which include clinical, electroencephalographic, and neuroimaging findings (Bien *et al.,* 2005). It has been suggested that an antibody-mediated immune response to neural cells plays a major role (Pardo *et al.,* 2004; Bien and Schramm, 2009). Although various antiepileptic drugs (AEDs), vagus nerve stimulation (VNS), immunomodulatory therapies including intravenous immunoglobulin (IVIg), pulse methyl-prednisolone, plasma exchange, and tacrolimus can all be used to treat RE, surgical treatments such as hemispherotomy or hemispherectomy are known to be the most effective methods of treatment (Bien and Schramm, 2009; Kwan *et al.,* 2010; De Benedictis *et al.,* 2013; Takahashi *et al.,* 2013; Granata *et al.,* 2014).

While electrical stimulation with implanted devices such as VNS and deep brain stimulation (DBS) are invasive methods, repetitive transcranial magnetic stimulation (r-TMS) and transcranial direct current stimulation (t-DCS) are non-invasive, brain stimulation methods used to treat patients with epilepsy (Morris *et al.,* 2013; Fregni and Pascual-Leone, 2007; Theodore and Fisher, 2007). t-DCS has been suggested to be a safe and promising method and it is generally accepted that low-dose direct electrical currents can be conducted transcranially (Nitsche *et al.,* 2002; San-Juan D *et al.,* 2015). Anodal stimulation increases cortical excitability while cathodal stimulation decreases it (Nitsche *et al.,* 2002; Brunoni *et al.,* 2012; Nozari *et al.,* 2014). Cathodal stimulation has been reported to decrease seizures in both humans and animal models, and is an alternative method to treat drug-refractory seizures (Fregni *et al.,* 2006a; Liebetanz *et al.,* 2006; Kamida *et al.,* 2011; San-Juan *et al.,* 2011; Varga *et al.,* 2011; Yook *et al.,* 2011; Faria *et al.,* 2012; Auvichayapat *et al.,* 2013; Kamida *et al.,* 2013; Zobeiri and van Luijtelaar, 2013; Parazzini *et al.,* 2014, San-Juan *et al.,* 2015). There are no reported studies of anodal stimulation in humans with epilepsy and only a single study evaluating the effect of anodal t-DCS in rats, in which it was reported that anodal stimulation had no effect on the threshold. No deleterious effects were reported (Liebetanz *et al.,* 2006).

Moreover, there is only one report with two patients regarding the positive effect of t-DCS on RE (San-Juan *et al.,* 2011; San-Juan *et al.,* 2015). Our aim was to investigate seizure characteristics of RE patients after cathodal t-DCS treatment, and further assess the safety of this technique, and compare it with that of anodal and sham stimulation.

Methods

Five patients (median age: 19±7; 3 females), who fulfilled the suggested criteria and were diagnosed with RE according to their typical clinical, EEG, and neuroradiological findings, were included in the study after providing their signed informed consent (Bien *et al.,* 2005). The study protocol was approved by The Ethical Committee of Istanbul University.

All patients included in the study had taken IVIg before the t-DCS trial (*table 1*). Patients 1, 3 and 4 had also taken pulse steroid treatment. Neither of these treatments showed any positive effect on seizure frequency or severity and were not used during the study period. Patients had started to fill in seizure diaries for three months before the study started and continued after the end of the study for two months. Their AEDs were not changed during the study period.

For this descriptive study of a small case series, sequences of stimulations were cathodal, anodal, and sham stimulation, in this order. Each of the consecutive stimulation types, cathodal, anodal or sham, were given with at least two-month intervals in order to avoid prolonged effects of the previous stimulation. Two types of cathodal stimulation were used with the same electrode montage:

– classic cathodal stimulation (Patients 3-5);

– an amplitude-modulated form of cathodal stimulation (Patients 1 and 2).

For classic t-DCS (DC), current was set to 2.0 mA. For modulated t-DCS, sinusoidal direct current with 0.85-mA peak-to-peak intensity was added to 1.15-mA direct current, as shown in *figure 1*. Its frequency was chosen as 12 Hz which is in the upper alpha range.

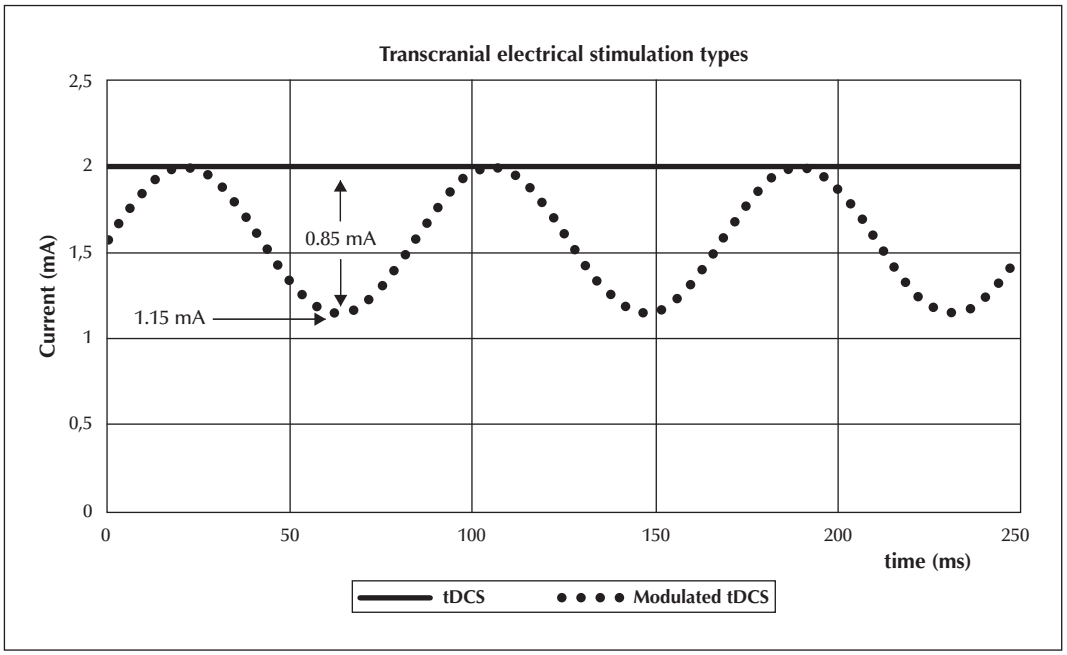

Figure 1. Two types of transcranial electrical stimulation. Transcranial direct current stimulation (t-DCS) and modulated transcranial direct current stimulation (mt-DCS) at 12 Hz. The offset current of mt-DCS was 1.15 mA and peak-to-peak current was 0.85 mA.

Furthermore, all patients received anodal stimulation with amplitude modulation. All patients and their relatives were blindfolded to the type of applied stimuli. We used custom built stimulators during the experiments. Testi (Teknofil Ltd., Istanbul, Turkey) can deliver microprocessor-controlled current, adjustable from 0 to 2 mA DC, and an alternative current (AC) component can be adjusted from 0 to 1 mA maximum, from 0.1 Hz to 22 Hz. Peak value of the superposed current delivered is 2 mA maximum. This stimulator cannot supply gradually increasing or decreasing current tails. In order to eliminate any itching or tingling sensations, we used a new version of the stimulator tessaNova (Teknofil Ltd., Istanbul, Turkey), which provides a ramped current waveform option. The tessaNova can deliver 4-mA maximum current, and within that limit, the AC component can be programmed from 0 to 2 mA, up to 200 Hz.

Maximum current density was calculated to be 57 uA/cm2 or 571 mA/m2, using 70 mm x 50 mm wet sponge electrodes with a 2-mA maximum, current-controlled stimulator. Maximum charge density was 1,028 C/m2 for a 30-minute stimulation period. For the modulated waveform, 0.85-mA peak-to-peak current was summed to 1.15 mA DC current. RMS value of the sinusoidal current component was 0.601 mA, which when added to the DC component, gave a 1.75-mA time average. Thus, using the same size of sponge electrodes, maximum current density was 500 mA/m2 and maximum charge density was 900 C/m2 for the 30-minute stimulation period. The calculated values were reported to be safe (Merrill *et al.,* 2005; Bikson *et al.,* 2009; Liebetanz *et al.,* 2009).

Saline-soaked sponge electrodes were used (electrode area: 35 cm^2). Patients received each of anodal, cathodal, and sham stimulations for 30 minutes. We used active electrodes over the mostly affected area and reference electrodes over the contralateral mastoid region. An active electrode was placed over the most prominent epileptogenic focus which was determined by an experienced clinical neurophysiologist during repetitive routine EEGs performed according to the international 10-20 system. EEGs were performed at the start of the study and all other previous EEGs of the subjects were evaluated to determine the most frequent focus (by counting relevant spikes during 30 minutes of routine EEG) in cases with multifocal discharges.

For anodal stimulation, an anode electrode was placed over the target zone and cathode was placed over the contralateral mastoid (same montage with opposite polarity). Three patients (Patients 2, 3 and 5) received sham stimulation for 60 seconds which was gradually decreased in the last 15 seconds with the same electrode montage as for cathodal stimulation.

Results

Subjects included in this study were between 11 and 26 years of age (median: 19±7). All patients had atrophy of one hemisphere and epilepsia partialis continua (EPC), besides other typical features of RE (*figure 2*).

Table 1. Demographic, clinical, EEG, and neuroimaging characteristics of the study group.

Patient	Sex	Age at onset (years)	Age at tDCS (years)	Seizure type	Neurological examination	EEG	MRI	Current therapy	Previous therapies	Follow-up time (months)
1	F	9	12	Left focal + EPC	Left pyramidal signs + cognitive deterioration	Right centro-temporal and frontal spike-and-wave discharges	Right hemisphere atrophy	LEV, OXC, TPM, LTG	PGN, pulse steroid, IVIg	20
2	M	13.5	22	Left focal + EPC + generalized and right focal	Left pyramidal signs + cognitive deterioration	Generalized slowing and left fronto-central and secondary generalized epileptiform discharges	Right hemisphere atrophy	LEV, CBZ	VGB, PB, IVIg	20
3	F	4	11	Left focal + EPC	Moderate motor impairment	Right fronto-centro-temporal epileptic discharges	Right rolandic, parietal and occipital atrophy	CBZ, CLB, LEV, VPA	OXC, LTG, ACTH, pulse steroid, IVIg	15
4	F	7	20	Left focal + EPC + secondary generaliza-tion	Left pyramidal signs	Epileptic activity over right fronto-central region, later diffusing over left hemisphere	Right hemisphere atrophy prominent in frontal lobe	LEV, VPA	IVIg, pulse steroid	12
5	M	8	26	Right focal + EPC	Right pyramidal signs	Slowing of the background activity and multifocal epileptic activity over the left hemisphere	Left hemisphere atrophy	LEV, VPA, CBZ	PGN, IVIg	12

EPC: epilepsia partialis continua; LEV: levetiracetam; OXC: oxcarbazepine; TPM: topiramate; LTG: lamotrigine; CBZ: carbamazepine; CLB: clobazam; VPA: valproic acid; PGN: pregabalin; VGB: vigabatrin; PB: phenobarbital; ACTH: adrenocorticotropic hormone; IVIg: intravenous immunoglobulin.

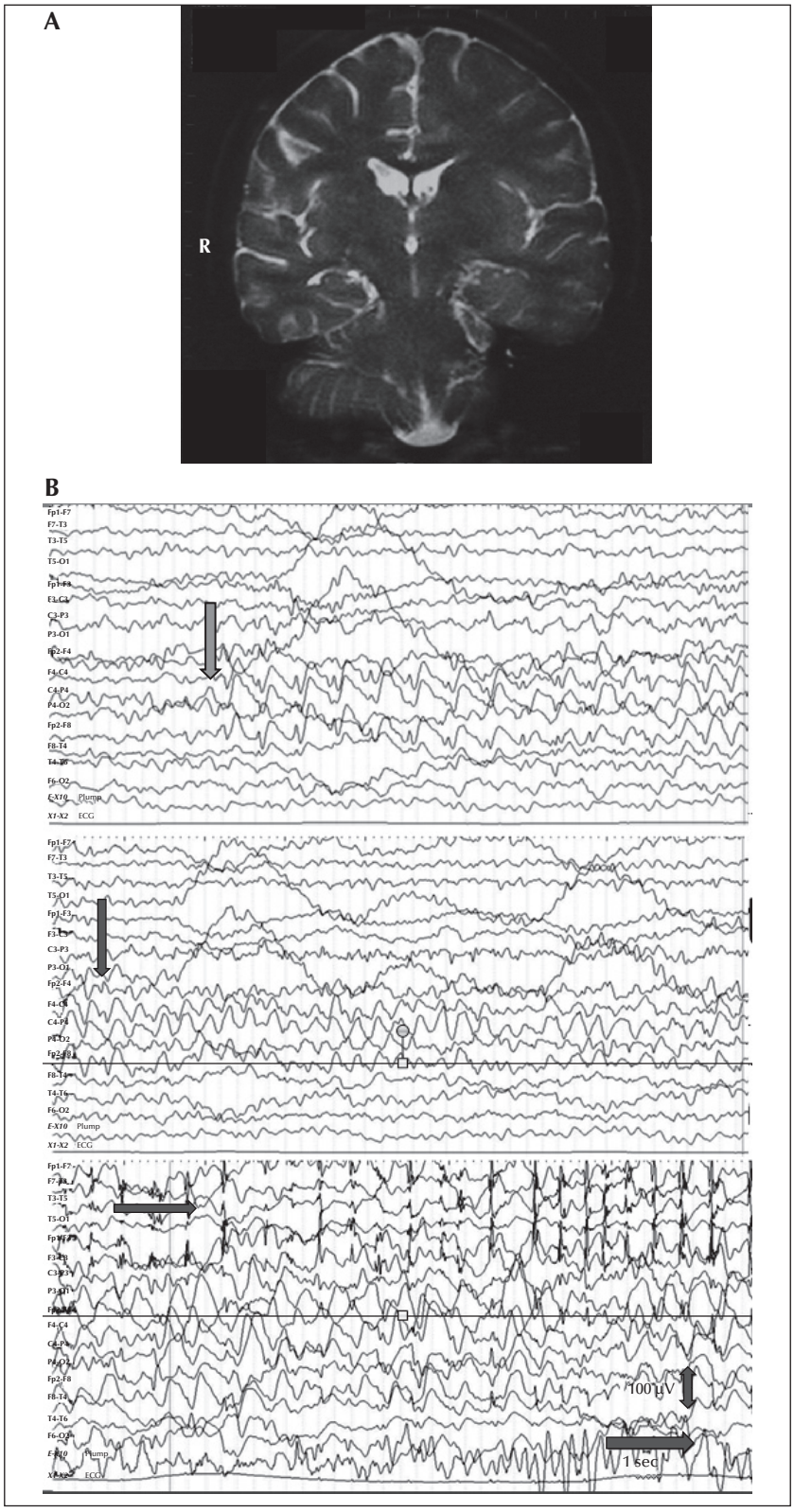

Figure 2. (A) Typical coronal T2-weighted MRI finding of Patient 4 showing diffuse right hemisphere atrophy. (B) Ictal EEG of Patient 4 showed right fronto-central rhythmic 2-Hz spike-wave activity (arrow; upper panel) with build-up into 4-Hz rhythmic theta patterns (middle panel) during twitching of the left side of her mouth. Seizure activity then spread into the left hemisphere (lower panel). Filters: low frequency: 0.5; high frequency: 70 Hz; notch filter.

Patient 1 and 2 had moderate cognitive impairment while other patients were severely affected, as shown by neuropsychological testing. Demographic, clinical, EEG, and neuroimaging findings of all patients are presented in *table 1*. Their routine laboratory findings, including haemogram, liver function tests and electrolytes, were within normal limits. Patients 1 and 3 also underwent metabolic disease screening because of their early-onset age, which revealed normal results. All patients, with the exception of Patient 5 (2 males and 2 females; 80%), had a greater than 50% decrease in seizure frequency in response to cathodal stimulation. Two patients (Patients 1 and 2) who received modulated cathodal t-DCS had better results. Patient 1 had eight days of seizure freedom despite her previous frequency of 20-30 seizures/day (94.5% seizure reduction) and Patient 2 also had 10 days of seizure freedom with a seizure reduction of 75% based on monthly seizure counts. The longest positive effect of t-DCS lasted one month.

On the other hand, after anodal stimulation and sham stimulation, patients did not report any improvement, according to their seizure diaries. No adverse effect was reported. Patient 5, who could not fill in the seizure diary during follow-up because of poor compliance, had reported no change in his seizure frequency in response to anodal, cathodal, or sham stimulation. We investigated this patient's clinical and EEG characteristics and could not find any clue to clarify his refractoriness to t-DCS therapy.

The changes of seizure frequencies after t-DCS are shown in *figure 3*.

During the first month of cathodal t-DCS, three patients reported to be more awake and went to school and attended lessons, according to the reports of their caregivers.

Discussion

Our small series suggested that cathodal t-DCS may be an effective adjunctive method for improving seizure outcome in RE patients. Although surgery is accepted as the most effective method for the treatment of RE, there are associated complications such as aseptic meningitis, sepsis, subdural haematoma, and perioperative bleeding (Granata *et al.*, 2014). VNS has also been shown to be effective in a few case reports with RE; reduction in seizure frequency to around 50% was reported in an adult-onset RE patient, and an 11-year-old boy had a six-month EPC-free period after VNS (Grujic *et al.*, 2011; De Benedictis *et al.*, 2013). Evidence-based studies proving the efficacy of this semi-invasive and expensive therapy for RE are still lacking. However, these anecdotal case reports have evoked interest in the possible effects of other stimulation techniques for RE.

Non-invasive brain stimulation techniques, such as r-TMS and t-DCS, have been studied regarding their effect on the modulation of cortical excitability and plasticity for many years (Nitsche and Paulus, 2009). Bindman *et al.* first showed the action of polarizing currents on the cerebral cortex of rats in 1964 (Bindman *et al.*, 1964). After this report, many studies were

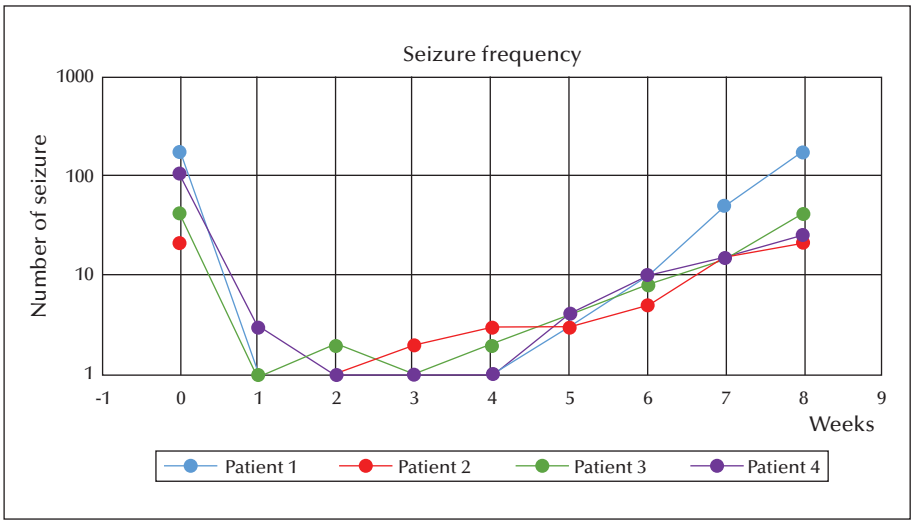

Figure 3. Weekly seizure frequency after cathodal stimulation in four cases with temporary prominent decreases in seizure frequency. Each colour represents a patient. Note that Patients 1 and 2 had modulated and Patients 3 and 4 classic t-DCS. The fifth patient, who reported no change in seizure frequency, is not included.

accomplished in order to investigate the effect of t-DCS over the human cortex (Hummel *et al.,* 2005; Fregni *et al.,* 2006a; Boggio *et al.,* 2007; Poreisz *et al.,* 2007; Ferrucci *et al.,* 2008; Reis *et al.,* 2008; Nitsche and Paulus, 2009). Cathodal t-DCS, which is shown to decrease cortical excitability, presumably works by reducing polarity-dependent cortical excitability shifts (Nitsche *et al.,* 2002; Nitsche and Paulus, 2009; Kamida *et al.,* 2013). Moreover, t-DCS changes synaptic space by affecting NMDA receptors or GABAergic activity (Brunoni *et al.,* 2012).

In recent years, t-DCS has evoked attention as a new non-invasive neuromodulation technique for refractory epilepsy. A recent literature review by San Juan *et al*. on animals and humans underlined the methodological, clinical, and statistical heterogeneity of the relevant studies (San Juan *et al.,* 2015). For the three animal and six human studies, the effect of t-DCS on epilepsy was investigated and all studies showed that subjects tolerated t-DCS well. In summary, two thirds of these clinical studies showed an effective decrease in epileptic seizures (Liebetanz *et al.,* 2006; Fregni *et al.,* 2006b; Kamida *et al.,* 2011; San Juan *et al.,* 2011; Yook *et al.,* 2011; Faria *et al.,* 2012; Auvichayapat *et al.,* 2013; Zobeiri and van Luijtelaar, 2013). The first randomized sham-controlled study of the effects of t-DCS on epilepsy was accomplished by Fregni *et al*. in 19 patients with refractory epilepsy and malformations of cortical development (Fregni *et al.,* 2006b). They placed the active electrode over the epileptogenic zone identified by baseline EEG, as in our study. The results of this study were replicated by others, showing reducing effects on seizures (Yook *et al.,* 2011). A study with the largest series including 36 children with focal epilepsy also showed that cathodal t-DCS can suppress epileptiform discharges for 48 hours, with a small decrease in seizure frequency (Auvichayapat *et al.,* 2013). This study used cathodal t-DCS with 1 mA for 20 minutes revealing a verum:sham ratio of 3:1 (Auvichayapat *et al.,* 2013). Our results are consistent with studies reporting positive effects of cathodal t-DCS for focal epilepsies.

There is only one previous study in the literature in which RE patients were investigated using t-DCS; this report of two cases with atypical adult- and adolescent-onset RE also showed a significant decrease in seizure frequency for 12 and six months, respectively (San-Juan *et al.,* 2011), however, this small report did not compare between the effects of cathodal t-DCS and sham stimulation. There are also methodological differences; we used 2-mA intensity for 30 minutes in three sessions, while the former study by San-Juan *et al*. used 1- and 2-mA intensity for 60 minutes in four sessions. We noted that the decrease of seizure frequency of our patients lasted for about only one month, whereas the former report showed a longer period of seizure freedom. These differences may reflect different stimulation protocols used, or be due to different characteristics of our severely affected, presurgical, childhood-onset patients with RE. Since none of our patients had undergone surgery before t-DCS and no drug alterations were made during this period, the decrease in seizure frequency may be solely attributed to the cathodal t-DCS effect.

The exact mechanism of action of t-DCS in epilepsy is unknown, but it is suggested that hyperpolarization and depolarization of axons, as well as alterations of synaptic functions, play a predominant role (San-Juan *et al.,* 2015). Blockage of sodium as well as calcium channels was shown to inhibit the effects of anodal stimulation, while blocking of glutamate receptors prevented the effects of t-DCS, regardless of directionality (Liebetanz *et al.,* 2002; Nitsche *et al.,* 2003).

EEG biofeedback is another non-invasive method used for self modulation of cortical electrical activity (increase or decrease) to treat the diseases related to cortical inhibition disorders (Tourette syndrome, attention deficit hyperactivity disorder, *etc.*). In the literature, a significant number of studies on EEG biofeedback training for treating different types of seizure disorders showed an improvement in seizure frequency (Tan *et al.,* 2009). Most of these studies aimed to increase sensorimotor rhythm (SMR) as induction of thalamic inhibitory functions resulted in success for epilepsy treatment. Our aim was to investigate not only the inhibitory effect of cathodal direct current stimulation, but also the possible influence of sinusoidal current frequency on the inhibition of cortex. Since the frequency of SMR is 12-15 Hz, the frequency of modulated current was chosen as 12 Hz to drive the SMR. In the present study, two different types of cathodal stimulation were applied, t-DCS and 12-Hz modulated t-DCS, and both showed positive effects on seizure frequencies. We believe that modulated cathodal stimulation may be more promising, however, this is based on our observations of only two patients, which may be biased.

Cathodal t-DCS, which decreases cortical excitability, targets the epileptic foci, whereas the modulated anodal t-DCS, which increases the effects of inhibitory connections, targets surrounding normal (physiological) cortical tissue. It has already been shown that trying to increase the SMR by EEG biofeedback helps to decrease cortical excitability (Lubar and Shouse, 1976). We argued that anodal stimulation at 12 Hz, which is in the upper alpha range and represents only a fraction of SMR, might help to reduce the intensity and frequency of seizures. This is why, in this study, we also tried to increase the inhibition in the surrounding normal cortex, in order to prevent the generation and the spread of the seizure. Electrode location for anodal and cathodal stimulation was the same because we believed that the epileptic foci were too small and

our stimulator electrodes covered both these loci and the surrounding normal cortical tissue.

t-DCS dosage is defined by current dosage, duration of stimulation, and electrode montage parameters (Brunoni *et al*., 2012). Although our study protocol is roughly consistent with that of previous studies, electrode size, intensity, duration of stimulation, number of repeated sessions, and intervals between sessions vary between all studies, and a worldwide consensus is needed for the use of t-DCS in epilepsy.

None of our patients reported side effects and they tolerated t-DCS very well. Thus, our protocol appeared to be safe and could be tried in a large number of patients with drug-resistant focal epilepsies in the future. Our primary aim was to investigate seizure frequency and repeated detailed neuropsychological tests after t-DCS sessions were not performed for these severely affected subjects. Another limitation of our study is the small number of subjects which is unavoidable in a single centre, for such a rare disease.

In conclusion, cathodal t-DCS is an effective method that can be easily and safely applied when compared to consistent life-long usage of many AEDs for RE. Although there is still a need for further sham-controlled, double-blind larger multi-centric studies, trying this non-invasive adjunctive method may be justified for cost-effectiveness and avoiding surgery complications. □

Supplementary data.
Summary didactic slides are available on the www.epilepticdisorders.com website.

Disclosures.
None of the authors have any conflict of interest to disclose.

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TEST YOURSELF

(1) What is transcranial direct current stimulation (t-DCS)?

(2) Why may direct current stimulation be tried among patients with Rasmussen encephalitis?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".