

tDCS clinical research - highlights: Epilepsy

Neuroelectrics White Paper WP201502

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Is transcranial current stimulation (tCS, including direct current, tDCS, alternating current, tACS, or random noise stimulation tRNS) effective for epilepsy? Under what conditions? With what montages?

Although the application of tDCS to epilepsy is intuitive from the neurophysiological point of view (tDCS can alter excitability of neural tissue), there are only a few papers on the subject, but they do provide interesting initial results. We have identified the following relevant papers which we include for further appraisals on a next future iteration.

We focus here on a compilation of the recent literature on this (quite wide) topic. We have relied on Google Scholar and also [PubMed](#) to carry out the search, including the terms of tDCS, tACS, tRNS (**from 2006 to March 2015**).

We advance that there is currently a high intensity in the research community probing this question in addition to using tCS for pure, fundamental research. As you can read below, there quite a few encouraging results in this area, although study group sizes (the famous N) are still relatively small. We try to highlight group sizes and the use of a sham-controlled, double-blind experimental technique. **The conclusion is that there is very interesting progress in this area, and that there is likely to be more in the future.**

In what follows we concentrate on interesting, study-oriented papers with patients, and leave fundamental research and reviews to the end. In order to make the reading lighter, we have freely edited the abstracts a bit (please click on the title link if you are interested in the paper).

META-ANALYSIS

San-Juan D, Morales-Quezada L, Orozco Garduño AJ, Alonso-Vanegas M, González-Aragón MF, Espinoza López DA, Vázquez Gregorio R, Anshel DJ, Fregni F, Transcranial Direct Current Stimulation in Epilepsy., Brain Stimul. 2015 Jan 13. pii: S1935-861X(15)00424-6.

Transcranial direct current stimulation (tDCS) is an emerging non-invasive neuromodulation therapy in epilepsy with conflicting results in terms of efficacy and safety. **OBJECTIVE: Review the literature about the efficacy and safety of tDCS in epilepsy in humans and animals.** We searched studies in PubMed, MedLine, Scopus, Web of Science and Google Scholar (January 1969 to October 2013) using the keywords 'transcranial direct current stimulation' or 'tDCS' or 'brain polarization' or 'galvanic stimulation' and 'epilepsy' in animals and humans. Original articles that reported tDCS safety and efficacy in epileptic animals or humans were included. Four review authors independently selected the studies, extracted data and assessed the methodological quality of the studies using the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions, PRISMA guidelines and Jadad Scale. A meta-analysis was not possible due to methodological, clinical and statistical heterogeneity of included studies. **RESULTS: We analyzed 9**

articles with different methodologies (3 animals/6 humans) with a total of 174 stimulated individuals; 109 animals and 65 humans. In vivo and in vitro animal studies showed that direct current stimulation can successfully induce suppression of epileptiform activity without neurological injury and 4/6 (67%) clinical studies showed an effective decrease in epileptic seizures and 5/6 (83%) reduction of inter-ictal epileptiform activity. All patients tolerated tDCS well. CONCLUSIONS: tDCS trials have demonstrated preliminary safety and efficacy in animals and patients with epilepsy. Further larger studies are needed to define the best stimulation protocols and long-term follow-up.

STUDIES

Assenza G, Campana C, Formica D, Schena E, Taffoni F, Di Pino G, Di Lazzaro V., Efficacy of cathodal transcranial direct current stimulation in drug-resistant epilepsy: A proof of principle., Conf Proc IEEE Eng Med Biol Soc. 2014 Aug;2014:530-3.

It has been proved that Transcranial DCS (tDCS) can modulate cortical excitability, enhancing or decreasing, respectively by anodal or cathodal polarity. The short-term and lasting alterations induced by tDCS are strictly related to the charge density, duration of stimulation and the depth of neuron below the skull. Epilepsy represents a pathophysiological model of unbalanced relation between cortical excitation and inhibition. In this line, tDCS can be exploited to counterbalance the neuronal hyper-excitation through electric neural modulation. This paper aims at providing the efficacy of cathodal tDCS in reducing seizures' frequency in drug-resistant focal epilepsy. The study was single blind and sham-controlled with an observation period of one month during which the patients or the caregivers provided a detailed seizures' calendar (frequency as n°/week; basal, post sham and post tDCS). Patients received sham or real tDCS treatment on the 8th and 22th days. **Two patients affected by focal resistant epilepsy were enrolled. They both underwent a consistent reduction of the seizures' frequency: about 70 % for Patient 1 and about 50% for Patient 2. This study represents the proof that cathodal tDCS may be efficient in reducing seizures' frequency in focal resistant epilepsy.**

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 Jul;6(4):696-700.

Cathodal transcranial direct current stimulation (tDCS) is a noninvasive brain stimulation method for suppressing regional cortical excitability. We examine the safety and antiepileptic efficacy of cathodal tDCS in children with refractory focal epilepsy. Although a prior cathodal tDCS trial in adults with epilepsy revealed EEG improvement, neither the antiepileptic potential nor the safety and tolerability of tDCS has been tested in children. **METHOD:** The study consisted of three phases: 1) a 4-week pre-treatment monitoring period with vital sign measures, EEG, seizure diary, and baseline quality of life (QOL) questionnaire; 2) a single treatment with 1 mA cathodal tDCS for 20 min with cathode positioned over the seizure focus and anode on the contralateral shoulder; 3) follow-ups immediately after stimulation, and at 24, 48 h, and 4 weeks after tDCS with continued seizure diary and epileptic discharge counts on EEG; the QOL questionnaire was also repeated 4 weeks after stimulation. Patients were randomized to receive either single session active or sham tDCS 1 mA, 20 min. **RESULTS: Thirty six children (6-15 years) with focal epilepsy were enrolled, 27 in active and 9 in sham group. All patients tolerated tDCS well. No serious adverse events occurred. Active tDCS treatment was associated with significant reductions in epileptic discharge frequency immediately and 24 and 48 h after tDCS. Four weeks after treatment, a small**

(clinically negligible but statistically significant) decrease in seizure frequency was also detected. CONCLUSION: A single session of cathodal tDCS improves epileptic EEG abnormalities for 48 h and is well-tolerated in children.

Faria P, Fregni F, Sebastião F, Dias AI, Leal A., Feasibility of focal transcranial DC polarization with simultaneous EEG recording: preliminary assessment in healthy subjects and human epilepsy., *Epilepsy Behav.* 2012 Nov;25(3):417-25.

We aimed to investigate the feasibility of an experimental system for simultaneous transcranial DC stimulation (tDCS) and EEG recording in human epilepsy. We report tolerability of this system in a cross-over controlled trial with 15 healthy subjects and preliminary effects of its use, testing repeated tDCS sessions, in two patients with drug-refractory Continuous Spike-Wave Discharges During Slow Sleep (CSWS). Our system combining continuous recording of the EEG with tDCS allows detailed evaluation of the interictal activity during the entire process. Stimulation with 1 mA was well-tolerated in both healthy volunteers and patients with refractory epilepsy. **The large reduction in interictal epileptiform EEG discharges in the two subjects with epilepsy supports further investigation of tDCS** using this combined method of stimulation and monitoring in epilepsy. Continuous monitoring of epileptic activity throughout tDCS improves safety and allows detailed evaluation of epileptic activity changes induced by tDCS in patients.

Varga ET1, Terney D, Atkins MD, Nikanorova M, Jeppesen DS, Uldall P, Hjalgrim H, Beniczky S., Transcranial direct current stimulation in refractory continuous spikes and waves during slow sleep: a controlled study., *Epilepsy Res.* 2011 Nov;97(1-2):142-5.

Cathodal transcranial direct current stimulation (tDCS) decreases cortical excitability. The purpose of the study was to investigate whether cathodal tDCS could interrupt the continuous epileptiform activity. **Five patients with focal, refractory continuous spikes and waves during slow sleep were recruited. Cathodal tDCS and sham stimulation were applied to the epileptic focus, before sleep (1 mA; 20 min). Cathodal tDCS did not reduce the spike-index in any of the patients.**

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 Feb; 47(2):335-42.

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. **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.