Efficacy Of Cathodal Transcranial Direct Current Stimulation In Drug-Resistant Epilepsy: a proof of principle

Giovanni Assenza, Chiara Campana, Domenico Formica, *IEEE Member*, Emiliano Schena, *IEEE Member*, Fabrizio Taffoni, *IEEE Member*, Giovanni Di Pino, and Vincenzo Di Lazzaro

***Abstract*—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.**

I. Introduction

Cerebral cortex has the ability to react to weak Direct Current Stimulation (DCS) with short-term and lasting alterations as was first invasively demonstrated in animals studies [1, 2]. Several authors proved that Transcranial DCS (tDCS) can modulate cortical excitability depending on the polarity of the provided electrical current: anodal tDCS enhances and cathodal tDCS decreases cortical excitability [3]. Further than from the polarity, the effects produced by the application of a weak direct current to brain are strictly related to the charge density (C\cm2) and to the duration of the stimulation. Moreover, the depth of the neuron below the skull and its orientation clearly influence the charge density required to modulate its firing. Remarkably, the zenith of the effect is reached well after the stimulation is ceased, thus unveiling the promotion of a plastic process that lead to the modulation, rather than a direct electrical phenomenon due to the current. The extent of this aftereffect is proportional to the total amount of delivered charge [4], despite the outcome of a standard spherical electric model of the human head implemented by a numerical method suggests that only about 10% of a scalp current of 2mA reaches the cortex [5].

All the above-mentioned features make tDCS a useful non-invasive neurostimulatory therapeutic technique that was historically first used in mental illness, but that today is applied to improving cognitive performance in healthy [6] and dement subjects [7] and modulate behaviors [8].

However, the brain disease that may be assumed as a model of an unbalanced relation between cortical excitation and inhibition is undoubtedly the Epilepsy. In this line, tDCS, that produces its effects solely through changes in membrane potential, can be exploited also in this pathology to counterbalance the neuronal hyper-excitation through electric neural modulation.

Epilepsy is the second most common neurologic disorder affecting up to 1% of the population. Mechanisms that underlies seizures are explained by hyper-excitability of neurons and hyper-synchrony of neuronal networks (neurons firing at the same time at a similar rate) that leads to clinical changes in motor control, sensory perception, behaviour, or autonomic function, according to the localization of epileptic source. The recurrence of unprovoked seizure, defined as Epilepsy, suggests that the brain has become permanently altered to produce abnormal, hypersynchronous neuronal firing. [9-11].

The common feature of antiepileptic therapies is thus the reduction of any pathological hyperactivity by either enhancing neuronal inhibition or reducing excitation. Although effective, currently available therapeutic approaches both medical and surgical have some drawbacks and do not solved every cases [12]. About 30 % of patients suffers of persistent seizures despite of an antiepileptic poly-therapy.

In these patients, promising results were obtained by vagal nerve stimulation (VNS) delivered by a stimulating electrode invasively implanted into the left vagal nerve in neck region. A diffuse inhibition of diencephalic cortex is the presumed pathophysiological pathways of VNS efficacy, but it is still under debate. Nevertheless VNS opened a new target window in epilepsy treatment for all that stimulations able to decrease cortical excitability.

Despite the encouraging background, there are few studies regarding the direct application of tDCS to epilepsy in humans [13-17].

G. Assenza, C. Campana, G. Di Pino, and V. Di Lazzaro are with the Institure of Neurology, Università Campus Bio-Medico di Roma, 00128 Rome, Italy. {g.assenza, c.campana g.dipino, v.dilazzaro}@unicampus.it.

E.Schena is with the Center for Integrated Research - Unit of Measurements and Biomedical Instrumentation, Università Campus Bio-Medico di Roma, 00128, Rome, Italy. e.schena@unicampus.it.

D. Formica, F.Taffoni, G. Di Pino, are with the Laboratory of Biomedical Robotics and Biomicrosystems, Università Campus Bio-Medico di Roma, 00218 Rome, Italy. {d.formica, g.dipino, f.taffoni}@unicampus.it.

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The present study aims to provide a proof of principle evidence that cathodal tDCS may be effective to reduce seizures' frequency in drug-resistant focal epilepsy.

II. MATERIALS AND METHODS

A. Study Design

The study was single blind and sham-controlled. The first week represented the pretreatment assessment phase for a systematic seizure count. Patients received, according to a pseudo-randomized order, the sham or the real tDCS treatment on the 8th and 22th days. The patients or the family/caregivers provided reliable, detailed seizures' calendar (frequency as n°/week) for all the weeks.

B. Direct Current Stimulation

Direct current was transferred by a saline-soaked pair of surface sponge conductive electrodes (3.5 cm x 3.5 cm) and delivered by a battery-driven, constant-current stimulator (Schneider Electronic, Gleichen, Germany- Newronika). Since cathodal stimulation decreases cortical activity, the cathodal electrode has been placed over the epileptogenic focus and the anode electrode over the contralateral homologous region.

During the real session a constant current of 1 mA intensity was applied for 9 min. Subjects felt the current as an itching sensation at both electrodes at the beginning of the stimulation. The current intensity was measured by an amperometer (or multimeter). Sham stimulation was performed by delivering current only for 10 s both at the beginning and at the end of the session, in order to cause the same initial itching sensation. No current was delivered for the rest of the stimulation period. This procedure allowed us to blind subjects for the respective stimulation conditions [18]. In both enrolled patients the first stimulation was the sham session and the second was the real one.

C. Patients

Two patients affected by drug resistant epilepsy, defined according to the International League Against Epilepsy (ILAE) guidelines [19], were enrolled. Patients (or their guardians) provided their informed written consent after formal approval of the study by the local ethics committee. Both patients underwent a standard electroencephalogram (EEG) to establish the epileptogenic focus according to the 10–20 system. There were no changes in antiepileptic drugs therapy during the whole observation period and in the six months before.

Patient 1.

Male, 24 years old. Affected by focal criptogenetic drug resistant epilepsy since the age of 4, mental retardation and obesity. He was in treatment with felbamate 1200mg twice a day and lamotrigine 200mg twice a day. He suffered from partial complex (PC) seizures, duration of 10-20 seconds, with a frequency of 10/week. Basal EEG showed bilateral synchronous and asynchronous fronto-temporal spikes-polispikes-and-slow waves. On the basis of clinical and EEG signs, T4 was chosen as epileptogenic focus.

Patient 2.

Male, 17 years old. He was affected by drug-resistant multifocal symptomatic epilepsy since the age of 7, mental retardation, type I diabetes, pigmentous retinitis. Brain MRI performed some years before showed a periventricular nodular heterotopia. His antiepileptic therapy was made up of Phenobarbital 100mg a day, carbamazepine 600mg twice a day, clobazam 10mg twice a day. He presented seizures with different semiology and a weekly frequency of 14 tonic-clonic (GTC, duration 20-30 seconds with long post critic phase) and 21 PC (few seconds of duration) seizures. According to clinical features and basal EEG, T5 was identified as the epileptogenic focus. Because of the presence of the multifocal epileptogenic activity, we placed the anode electrode over the cortical area presumed to be responsible for the most invalidating crisis.

III. RESULTS

Patient 1. Basal 10/week, post sham session 6/week, post tDCS session 3/week.

Patient 2. Basal 35/week, post sham session 27/week (11GTC and 16 PC), post tDCS session 18/week (5GTC and 13 PC). The seizure frequency of both patients is shown in Fig. 1.

Both patients underwent a consistent reduction of the frequency of the seizures. It was of about 70 % for Patient 1 and about 50% for Patient 2.

The amelioration is evaluated comparing of the frequency of seizures between the first week (before the first tDCS application) and the last week of the month (after the second basal condition and the after the second tDCS application).

Moreover, it has not reported any potential cathodal tDCS side effects, as the very common headache, fatigue, and nausea. The pharmacological therapies of both patients have not been modified during the month of the study.

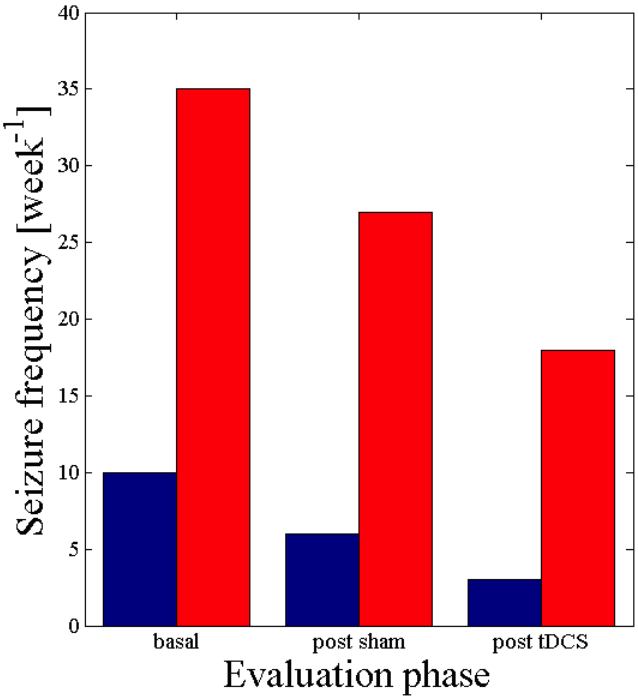

Figure 1. Seizure frequency of Patient 1 (blue bars) and Patient 2 (red bars) in the three evaluation phases.

IV. Discussions

This study represents the proof of principle that Cathodal transcranial direct current stimulation (ctDCS) is safe and efficient in reducing seizure frequency in drug-resistant epilepsy.

In our patients, a single session cathodal tDCS results in reducing seizure frequency when compared with basal and post-sham value in symptomatic focal epilepsy. Even if sample size was very limited, our data corroborate previous reports about the clinical use of ctDCS in epilepsy.

Particularly one study evaluated the efficacy of cathodal tDCS in epileptic patients [13] and it found a reduction of seizure frequency, even though not statistically significant, in nineteen patients with refractory epilepsy caused by neocortical malformation enrolled by a single clinical center. A more recent case report [14] referred about the efficacy of cathodal tDCS in suppress seizures in a drug resistant epileptic child. Finally, in 2012 Faria et al. [15] obtained a large reduction in interictal epileptiform EEG discharges in two patients with Continuous Spike-Wave Discharges During Slow Sleep.

The antiepileptic effect is presumed to involve a reduction of excitability in the cortex underlying the cathodal electrode and thus the excitability of epileptic neurons. This excitability downshift could reduce spontaneous hypersyncronous electrical activity of epileptic zone and the corresponding clinical manifestations. On the other hand, the duration of the clinical effect was very much longer that the proved inhibitory effect of ctCDS on cerebral cortex as assessed by standard instruments (transcranial magnetic stimulation), so that other antiepileptic local effects on the cortex should be inferred (e.g., inhibitory gene expression, long-term modification of membrane channels, cortical, etc). In this term, a so prolonged effect of tDCS was unexpected and trials with a high number of participants and a longer period of post-tDCS evaluation will be needed to definitively prove the potential clinical application of tDCS in clinical settings. Intensity, duration and inter-stimulation interval are further three features to modulate in the attempt to optimize this effect; in fact intensity is crucial for the deepness of the effect respect to the scalp, duration of the stimulation influences he duration of the after-effects and inter-stimulus interval may help in prolonging the desired effects itself.

V. Conclusions

tDCS represent a painless, safe, non-invasive method for focal brain stimulation and the present encouraging result may increase the interest regarding the possibility to use DC as an easy therapeutic option in epilepsy. Future efforts will be devoted to enlarge the sample size and confirm the present results.

Since only few studies are available so far, it remains still undefined the correct and standardizes methodology to apply tDCS.

Further investigation are needed to refine the stimulation parameters in order to identify the most effective for our scope. In particular, the optimal electrodes size and shape, duration of stimuli, the site of reference electrodes, the current intensity and the frequency of stimulation are the main parameters that should be defined.

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