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Transcranial direct current stimulation reduces intracerebrally-recorded epileptic seizures and behavioral disturbances

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In principle, epilepsy including recurrent seizures resulting from excessive neuronal discharges should be an ideal candidate for tDCS, expected to rebalance the cortical excitability. Transcranial direct current stimulation(tDCS) has been used in preclinical studies [1] and some of them have been translated to clinical studies for reducing the seizure frequency. In drug-resistant epilepsy, occurrence of epileptic discharges significantly decreased after several tDCS sessions compared to sham-controlled groups. Based on these results, a recent review proposed a level B recommendation ("probable efficiency") for tDCS in epilepsy [2]. However, the effect of tDCS on epileptic seizures in humans is largely unknown, due to difficulties in recording (unpredictability of seizure) and analyzing (noise and artifacts) scalp EEG signals during tDCS [3]. To our knowledge, one only one study attempted to prevent the generation of seizures in epileptic patients using tDCS, and this approach was not effective [4]. Here, thanks to a rare opportunity of simultaneous tDCS and intracranial EEG (iEEG) recordings, we investigated the effect of tDCS on focal epileptic seizure with direct and online video-iEEG recordings in a drug-resistant epileptic patient. With this rare dataset, our aim was to demonstrate that ictal epileptic discharges and clinical symptoms recorded during tDCS were significantly different and reduced as compared to those recorded without tDCS.

MC is a female (19-year-old) suffering from refractory insulo-opercular epilepsy. She gave informed consent to participate in this study (NCT03644732). Based on the presurgical evaluation, a video-iEEG recordings was planned to localize the epileptogenic zone (EZ) and the eloquent cortices around. The patient was stereotactically implanted with seventeen multi-contact iEEG electrodes (215 recording contacts) targeting the left hemisphere. HD-video iEEG recording was performed 20 hours a day for four days. Drug treatment remained stable during the iEEG evaluation. To target the EZ, a T7 (anode over the EZ [5]) - C6 (cathode) montage was chosen using two HD electrodes (12mm diameter). First, a bipolar transcranial alternating current stimulation (tACS) of 1mA amplitude was performed to quantify the induced electric field (EF) [6]. Second, a resting state session of transcranial direct current stimulation (tDCS) was performed to modulate the interictal epileptic discharges. The tDCS parameters were +1mA (T7) and -1mA (C6) and a 20-min total duration was set. Due to clinical considerations, TES were done the last day of the iEEG recording i.e., just before the removal of the intracerebral electrodes. The four-day of video-iEEG recordings were visually analyzed by the two epileptologists blind to the tDCS experiment. Datasets of iEEG signals were sorted into ictal epileptic discharges without tDCS (IED) and ictal epileptic discharges during tDCS (IED*). Same-sized epochs (12 seconds) were defined considering the mean seizure duration. FFT analysis of iEEG signals was performed using bipolar montage. The mean amplitude and standard deviation were computed for each frequency band ($\Delta - \theta - \alpha - \beta - \gamma1 - \gamma2$) of the different epochs. Then, a Friedman statistical test, with post-hoc pairwise Bonferroni corrections, was performed to compare all IED. The global percentage differences at the different frequency bands were calculated. In addition, the epileptogenicity of the brain structures was quantified using a semi-automatic calculation of the "epileptogenicity index" [7] (EI). Finally, clinical symptoms during the seizures were retrospectively reviewed by two epileptologists blind to the tDCS experiment using HD video recordings.

During the four days of iEEG investigation, five spontaneous seizures occurred and were recorded in S′1–2 to 8–9 and O′5–6 to O′9–10 contacts (Fig. 1A; Supplementary Fig. 1) i.e., the posterior long insular gyrus and the basal part of the parietal operculum. Strikingly, IED durations were 35–37 seconds long whereas IED* was 12 seconds long ($p < 0.001$; Student's T-test). Mean EF magnitudes in the EZ ranged from 0.18 to 0.21 V/m. At the beginning of the seizures (Epoch A), no significant amplitude spectrum difference was found between IED* and all other IED. During epochs B and C, IED* amplitude distributions were significantly higher than the four IED in the delta, theta, and alpha bands. In higher frequency bands (beta, gamma1 and gamma2), the amplitude spectrum distributions of the IED reversed and became significantly lower than the IED*. In the last segment D, no significant difference was found (Fig. 1B; Supplementary Table 1). The epileptogenic index of IED* was null in all bipolar contacts whereas from 4 to 5 bipolar contacts were significantly detected with EI > 0.3 for the four IED (Supplementary Fig. 2 and table 2).

For the first four epileptic seizures, the first clinical symptom was facial reddening and the patient verbally warned. Then, she had a right upper limb tonic extension, a body rotation, a head flexion, a left lower and upper limb tonic extension. Finally, the patient smiled. The duration of the clinical symptoms was 37, 40, 36, 36 seconds. For the seizure recorded during tDCS, the beginning and the end were like the first four epileptic seizures. However,

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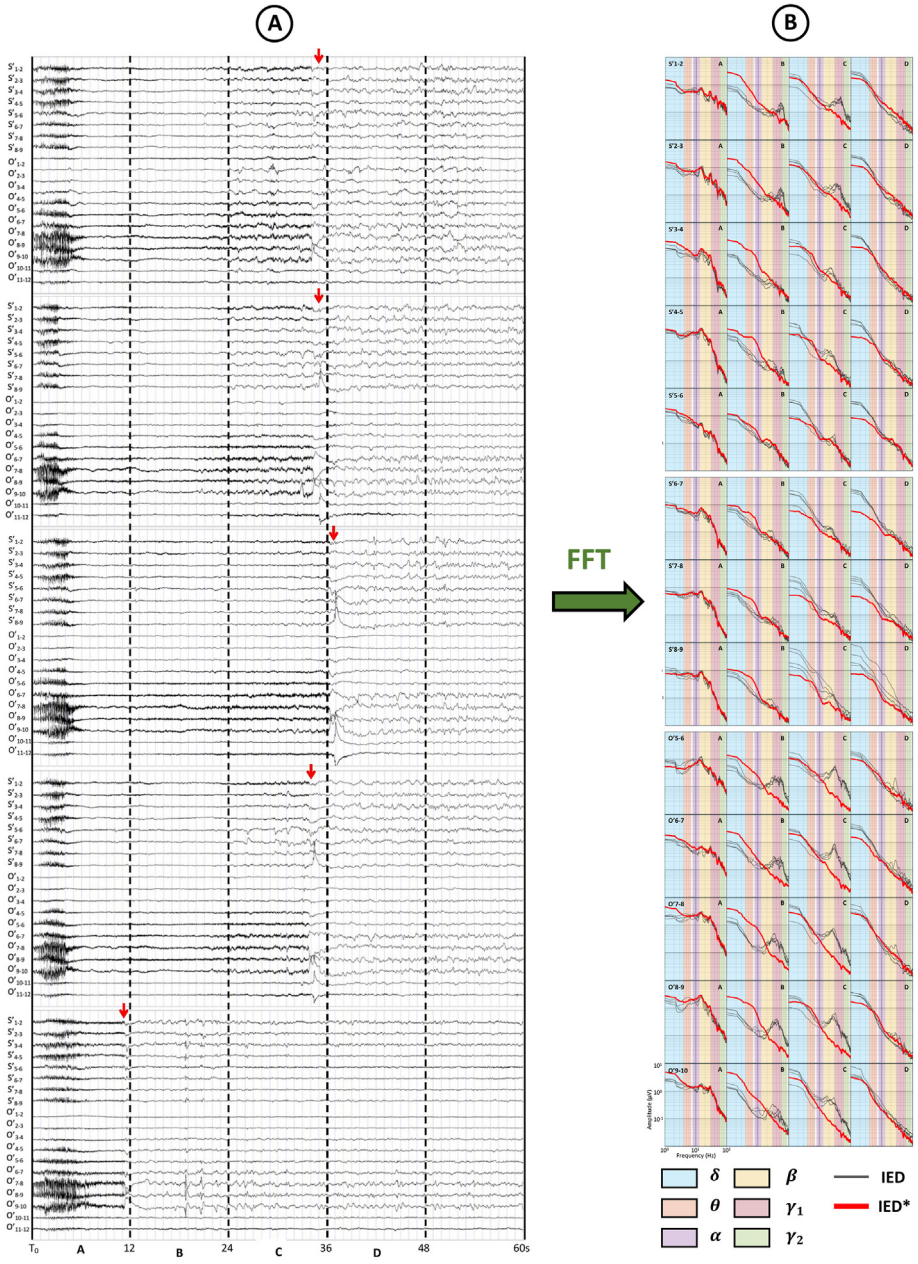

Fig. 1. A. iEEG signals in bipolar montage of selected contacts in the epileptogenic zone (S′ and O′ electrodes). The five epileptic seizures started with polyspike discharges in the β band (period A). Then, for seizures 1–4, low amplitude fast discharges occurred in the γ**1** band (B and C periods) and seizures stopped after around 36 sec. In contrast, seizure #5, recorded during tDCS, stopped after 12s and no amplitude fast discharges was observed. (Red arrow: end of the ictal epileptic discharges). **B.** Amplitude spectrum of the IED* (red line) compared to the IED (n = 4; gray lines) in the epileptogenic zone (O′5–10; S′1–9 iEEG contacts). The different frequency bands are colored (cyan: δ band; orange: θ band; purple: α band; yellow: β band; red: γ_1 band; green: $\gamma_2$band). IED: ictal epileptic discharge; * mentioned that the discharges were recorded during tDCS. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

strikingly, the major disabling motor symptoms disappeared (Supplementary Fig. 3). The duration of this seizure during tDCS (22 seconds) was significantly reduced ($p = 0.005$, Student's T-test).

Thanks to this rare dataset, we provide here original evidence of both electrophysiological and clinical epilepsy symptoms reductions during a single tDCS session at low intensity and for few minutes duration. Our report is important because it offers both fundamental insights in the intra-cortical effects of tDCS on epileptic discharges and therapeutic perspectives. The most crucial feature of the epileptic seizure, i.e., the low amplitude fast discharge, was completely cancelled and the most disabling and dangerous part of the clinical symptoms disappeared. Regarding the underlying mechanism of the tDCS-related seizure reduction, the main hypothesis would be the inhibition of the EZ i.e., a reduction of cortical hyperexcitability and thus of the ability of cortical tissue to produce a high-energetic fast epileptic discharge. Since the seizures during and without tDCS were identical during the pre-ictal period but then differed in terms of absence of the low-voltage fast discharge, the tDCS effect could be more precisely related to a neuromodulation of the interneurons. Indeed, several studies have shown that interneuron activity leads to the

generation of low-voltage fast discharge observed at the seizure onset [8–10].

Author contributions

L.K. – Initiation; Conceptualization; Ethics Approval; Data recording and analysis, Manuscript writing, Figures, Funding acquisition, Scientific supervision; S.L.- Electric field measurements, Computational modeling, Data analysis, Manuscript writing, Figures; J.P.V - Ethics Approval, Clinical and diagnostic neurological procedures; J.J - Ethics Approval, Neurological diagnostic procedures; S.C.C – Ethics Approval, Intracerebral electrodes implantation, Epilepsy surgery, Medical patient care; L.T. - Ethics Approval, Visual expertise of video, Neurological diagnostic procedures, Medical patient care; J.D. – Initiation, Electric field measurements and computational modeling, data analysis, TES protocol; L.G.M – Ethics Approval, Conceptualization, Visual expertise of video, Neurological diagnostic procedures, Medical patient care, Medical supervision (Head of the epilepsy unit)

Data sharing

Original data of this study are available (https://doi.org/10.17632/3krd4hrk86.2).

Declaration of competing interest

JD has patent rights to HD-tDCS technology.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2023.03.040.

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