Transcranial Direct-Current Stimulation as Treatment in Epilepsy

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Summary

Transcranial direct-current stimulation (tDCS) is a widely explored and easy to use technique of non-invasive neuromodulation, which has shown both excitatory and inhibitory effects, depending on the direction of the current flow. Cathodal stimulation has an inhibitory effect on multiple cortical levels, which is of particular interest for the use as treatment of epilepsy. Here, we review the recent literature, especially of 2016, and discuss the important aspects of tDCS, including patient selection, stimulation localization, and evaluation of treatment success, as well as safety, and regulatory aspects.

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Keywords: Epilepsy, transcranial direct-current stimulation, tDCS, outcome, drug therapy

Transkranielle Gleichstromstimulation als Behandlungsoption bei Epilepsie

Transkranielle Gleichstromstimulation (tDCS) ist eine weitverbreitete und einfach zu bedienende Methode der nicht-invasiven Neuromodulation. Je nach Richtung des Stromflusses hat sie exzitatorische oder hemmende Effekte gezeigt. Kathodale Stimulation hat eine kortikal hemmende Wirkung auf mehreren Ebenen, was von besonderem Interesse ist für die Verwendung bei der Behandlung von Epilepsie. Hier besprechen wir die neuere Literatur, insbesondere des Jahres 2016, und diskutieren die wichtigsten Aspekte von tDCS, einschliesslich Patientenauswahl, Lokalisierung der Stimulation und die Evaluation des Behandlungserfolges, sowie sicherheitstechnische und regulatorische Aspekte.

Schlüsselwörter: Epilepsie, transkranielle Gleichstromstimulation, tDCS, Behandlungserfolg, medikamentöse Behandlung

La stimulation transcrânienne à courant continu comme traitement d'épilepsie

La stimulation transcrânienne à courant continu (tDCS) est une technique de neuromodulation non invasive, largement explorée et facile à utiliser. En fonction de la direction du courant, elle a montré à la fois des effets excitateurs et inhibiteurs. La stimulation cathodique a un effet inhibiteur cortical à de multiples niveaux, ce qui est particulièrement intéressant pour l'utilisation dans le traitement de l'épilepsie. Ici, nous passons en revue la littérature récente, en particulier de 2016, et discutons les aspects importants autour de la tDCS, y compris la sélection des patients et la localisation de la stimulation, l'évaluation de l'efficacité du traitement, ainsi que les aspects de sécurité et de réglementation.

Mots clés : Epilepsie, stimulation transcrânienne à courant continu, tDCS, efficacité du traitement, traitement médicamenteux

Introduction

After the initial experiments of Luigi Galvani and Allessandro Volta in the 1790ies, it was discovered that weak galvanic current flowing through different parts of the body could have interesting "physiological effects", for example relief of musculoskeletal and nociceptive pain (nowadays called Transcutaneous Electrical Nerve Stimulation, TENS), or relief of mental disorders [1]. During the following centuries electrical stimulation of the brain was part of the psychiatrist's armamentarium, but was largely overshadowed by electroconvulsive therapy and the advent of psychopharmacologic drugs.

Only in the last two decades, this technique, now called transcranial Direct Current Stimulation (tDCS) was given new scientific basis by fundamental work that promoted growing interest in almost all neurological and psychiatric domains [2 - 5]. In 2016, a review listed 340 published studies (not counting single case reports) on clinical effect of tDCS in patients. TDCS

Figure 1. General Faradization: The physician uses himself as the conductor for the electrical current passing from the machine through to the patient who sits in a chair with his feet on a peddle (New York 1881). (https://collections.nlm.nih.gov/catalog/nlm:nlmuid-101436706-img)

was used in conditions such as mood disorder, schizophrenia, addiction and craving, autism, and attention disorders, tinnitus, pain, cerebral palsy, multiple sclerosis, epilepsy, consciousness disorders, neurodegenerative disorders and post-stroke disability [6]. Today, tDCS has become very popular, and its unsophisticated technique, easy management, and low cost allow an at home use of the device and even self construction by the user, which however raises ethical and legal questions concerning misuse.

A group of European experts recently reviewed the current evidence for therapeutic efficacy of tDCS in all neurologic and psychiatric domains [7]. Class I required studies on 25 patients or more (arbitrary number) having received tDCS treatment, Class II required 10 - 24 patients having received tDCS treatment. Level A (definite efficacy) could not be given for any indication. Level B recommendation (probable efficacy) was given for (1) anodal tDCS of the left primary motor cortex in fibromyalgia; (2) anodal tDCS of the left dorsolateral prefrontal cortex in major depressive episode without drug resistance, and in (3) anodal tDCS of the right DLPFC addiction/craving. Level C recommendation (possible efficacy) was given for anodal tDCS of the motor cortex in chronic lower limb neuropathic pain secondary to spinal cord lesion. On the other hand, Level B recommendation was given for the absence of clinical effects (probable inefficacy) for (1) anodal tDCS of the left temporal cortex in tinnitus; and (2) anodal tDCS of the left DLPFC in drug-resistant major depressive episode [7]. However, due to the absence of sufficient evidence, no recommendation could be given for migraine, postoperative pain, Parkinson's disease, dystonia, motor stroke, multiple sclerosis, disorders of consciousness, Alzheimer's disease, schizophrenia and epilepsy.

The neurophysiological effect of tDCS

It is important to understand that tDCS applies weak direct-current, which does not induce neuronal firing but modulates the neuronal membrane potentials and alters the cortical activity and excitability [8]. The applied constant electric field induces prolonged neurochemical changes by displacing polar molecules, neurotransmitters and receptors along the cerebral tissue [9, 10], and the current flow provokes a direction (polarity) dependent shift of the membrane potential [2, 11]. Enhanced excitability means an increase of the responsiveness of the neuron to afferent synaptic inputs [12, 13], of the neuronal firing at the surface positive electrode (or decrease at the surface negative electrode) as well as of the size of evoked potentials [14]. Cathodal stimulation (negative, the current flows outwards) leads to cortical inhibition, whereas anodal stimulation (positive, the current flows inward) leads to cortical facilitation with an increase of cortical excitability [5, 15, 16].

Several new studies have recently shed more light on the partially understood effects of tDCS on the cellular targets such as excitatory neuronal somas, axons, dendrites, interneurons, glial cells, and endothelial cells. Neuronal excitability can only be evaluated within subcellular regions because neurons are always simultaneously depolarized and hyperpolarized [17].

For example, using rat hippocampal brain slices and computational modeling, a new study [18] shows that tDCS modulates the likelihood of neuronal firing for a given and fixed synaptic input in an asymmetric way, as under anodal stimulation the opposing polarization of soma and dendrite have a synergistic effect and increase both the spiking probability at the soma as well as the driving force of synaptic activity. Under cathodal stimulation, these opposing effects neutralize each other.

Another new study investigated how tDCS produced task-specific lasting enhancements when applied during training [19]. They analyzed the effects of the application of cathodal and anodal stimulation during plasticity induction of long-term potentiation (LTP) and depression (LTD) at synapses in rat hippocampal slices (between Schaffer collaterals and CA1) in apical and basal dendritic compartements. They showed that both cathodal and anodal stimulation reduced LTD in apical dendrites, but that cathodal stimulation enhanced LTP in apical dendrites while anodal stimulation enhanced LTP in basal dendrites.

In a third study, one-week lasting increases in hippocampal LTP, learning and memory was measured in mice after 20 min of tDCS [20]. These effects were associated with enhancement of acetylation of Brain-Derived Neurotropic Factor (BDNF) at several levels and enhanced phosphorylation of the C-AMP Response Element-Binding (CREB) protein, suggesting that anodal tDCS increases hippocampal LTP via chromatin remodeling of BDNF regulatory sequences that lead to increased expression of this gene. This gives support to the use of tDCS for the treatment of brain diseases with impaired neuroplasticity, such as Alzeimer's disease and dementia [21, 22], Huntington's disease [22, 23], depression [24, 25], schizophrenia [26], obsessive-compulsive disorder [27], Rett syndrome [22, 28], or anorexia nervosa [29], and it might also explain the effect of tDCS in patients with epilepsy [30, 31].

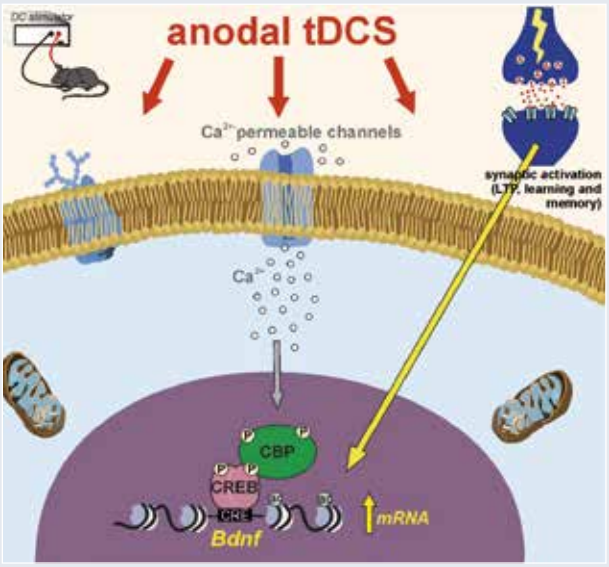

Figure 2. Anodal tDCS (positive, the current flows inward) leads to cortical facilitation with an increase of cortical excitability. The mechanism is via a transient increase in intracellular calcium (Ca2+), which initiates molecular cascades that lead to persistent changes in chromatin structure of the Brain-Derived Neurotropic Factor (BDNF), including the phosphorylation of the C-AMP Response Element-Binding (CREB) protein and the recruitment of the CREB-Binding Protein (CBP). As a result, long term potentiation (LTP), as well as learning and memory cause an increased transcription of BDNF [20].

tDCS has promising antiepileptic effects

Five different approaches of brain stimulation are available for treatment of epilepsy, of which today only two are approved in Switzerland, namely Deep Brain Stimulation in the Anterior Thalamic Nuclei (DBS-ANT) and Vagal Nerve Stimulation (VNS). However, Transcranial Magnetic Stimulation (TMS), transcutaneous Vagal Stimulation (tVNS), and tDCS are still in experimental state. So far, the missing evidence of tDCS efficacy in treatment of epilepsy is most likely due to the heterogeneity of the studies (i.e. different stimulation protocols and patient population). In our recent literature review (march 2016 [32]), we found 47 publications of which we counted six case reports [33 - 38] and three sham controlled studies [39 - 41]. In 2016, two new studies were published on patients with mesial-temporal lobe epilepsy and hippocampal sclerosis. One was a randomized placebo-controlled, double-blinded clinical trial in 28 adult patients [42], which compared 2mA cathodal tDCS over the epileptic focus during 30 minutes in three consecutive days versus five consecutive days versus placebo stimulation. Seizure frequency and interictal epileptiform discharges (IEDs) were quantified before and after treatment, as well as at 30 and 60 days follow-up. There was a significant reduction of seizure frequency at 30 ($p = 0.001$) and 60 days ($p = 0.0001$) compared to baseline (mean reduction -48%). The reduction was also greater in the five-days group compared to the three-days group. Also a significant short-term reduction of IED was found between baseline and immediately after interventions ($p = 0.041$) in all groups [42]. The other study compared in a cross over design the effect of modulated cathodal stimulation (2mA for 30 min on 3 consecutive days) to sham stimulation in 12 patients [43]. Sham was designed as a short 60 s stimulation that then decreased during 15 s, while the electrodes stayed for 30 minutes over the stimulation site. The mean seizure frequency decreased from 10.58 to 1.67 per month after cathodal tDCS application ($p = 0.003$), and ten patients (83.33%) had more than 50% decrease in their seizure frequency. Six patients (50%) were seizure-free one month after the cathodal tDCS session. However, two patients (16.67%) also showed positive sham effects [43].

Over all, we count now a total of 157 patients that were studied in clinical trials, most of which suffered from mesiotemporal lobe epilepsy (with or without hippocampal sclerosis, N = 89, 56%) [41 - 44], followed by dysplasia (N = 23, 20%) [45]. The other studies investigated single patients with Rasmussen's encephalitis [34, 35], continuous spikes and waves syndrome during slow sleep (CWSW) or Landau-Kleffner Syndrome [33, 36, 37], epilepsy from vascular lesions (N = 17).

tDCS also was evaluated in pediatric population. Although in some studies in patients with CSWS promising results were reported [33, 37], a double-blinded and sham-controlled crossover study in five pediatric

patients with CSWS failed to show a decrease of epileptiform activity with cathodal tDCS [36]. However, suppression of interictal spikes for the duration of 48 hours, together with a small but significant decrease in seizure frequency (-4.8%) during the following four weeks was found in a randomized sham-controlled, unblinded study on 36 children with focal epilepsy (of undefined origin) [40]. Also in 22 children with Lennox-Gastaut syndrome, cathodal stimulation over the motor cortex combined with pharmacologic treatment reduced seizure frequency and IEDs [46].

Regulatory aspects of tDCS

In 2016, a group of experts proposed technical guidelines to ensure a proper and risk free use of tDCS protocols [47]. The safety profile of tDCS is extremely high, if the currently recommended stimulation protocols are respected (stimulation time under 40 min, current under 4 mA, electrical charge under 7.2 Coulombs) [48]. There are only very limited adverse effects, such as local sensory discomfort or mild headache [47 - 49]. Not any serious adverse effect has been reported in more than > 50'000 subjects described in the 340 publications using tDCS in patients [6].

Data from relevant animal models indicate that brain injury by tDCS occurs at predicted brain current densities (6.3 - 13 A/m^2) that are over one order of magnitude above those produced by tDCS respecting the guidelines on humans. Moreover, the large body of treated patients included all kinds of neurologically vulnerable individuals, such as children, elderly, patients suffering from stroke, mood disorders, and epilepsy [48].

In practice, a good contact between electrodes and skin across the whole electrode is important, provided by the use of a gel, cream, or appropriately large, wet electrode, in order to limit excessive current density (which depends on electrode size and shape) and local skin burns [50, 51].

From the regulatory point of view, because tDCS is not yet approved as a treatment for epilepsy, it falls under the requirements for clinical investigations with medical devices. In Switzerland, the requirements for such reseach carried out prospectively on patients is regarded as clinical trial with medical devices and described by the Human Research Act (HRA 810.30) [52], and Clinical Trials Ordinance (ClinO 810.305) [53], which are the integration of the European regulations into Swiss national laws.

In order to start such a clinical study, the following requirements must be met: Stimulation devices that are not certified for conformity with European standards ("CE marked") must be considered as investigational devices, meaning that, apart from the aspects related to clinical evaluation, a proof of their compliancy with the essential requirements of the European Medical Device Directive (DIR 93/42/EEC) is requested. Currently, many of the tDCS devices available on the market are not approved for human use in Europe. Furthermore, the clinical study documentation must be prepared in compliance with the ISO 14155 standard for clinical investigations (Good Clinical Practice) and needs to be approved by both the competent authority (Swissmedic) and the competent Ethics Committee (Swissethics).

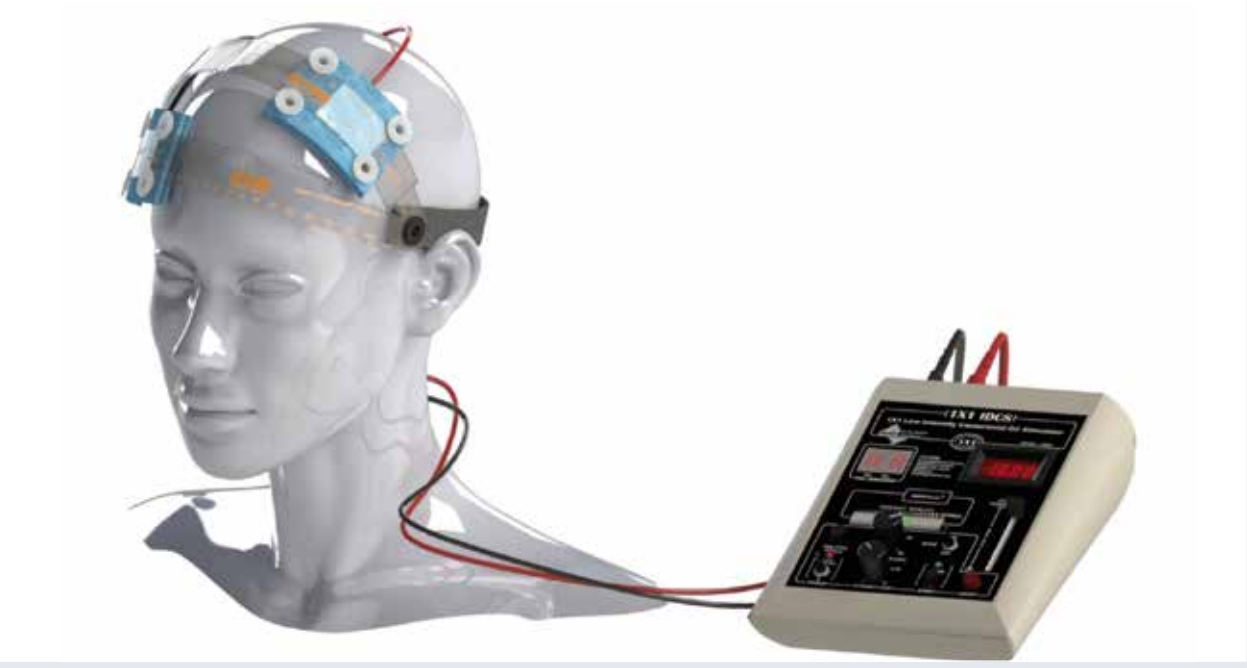

Figure 3. Example of a typical tDCS device comprising the stimulation unit, and 2 sponge electrodes of 5 x 7 cm, mounted on the head with a system of stripes. (http://soterixmedical.com/research/1x1).

Careful patient selection

In order to create a homogenous group of patients with the same epilepsy type and localization, patient selection warrants careful consideration. Drug studies have shown that 40 - 50% of patients with focal epilepsy (restricted to one hemisphere only) and about 15% of patients with idiopathic generalized epilepsy (concerning both hemispheres) are refractory to pharmacologic treatment.

"Drug resistant epilepsy" is defined as the absence of complete seizure control despite regular drug intake of 2 or more antiepileptic drugs (AEDs) up to sufficiently high dosages (serum drug level control). With the prescription of a 3rd AED the probability to obtain seizure control increases for not more than 2% [54]. Only in case of drug resistant epilepsy further treatment options need usually to be explored, i.e. epilepsy surgery or neuromodulation. TDCS will come into play only in patients with intractable epilepsy that are not eligible for epilepsy surgery or don't opt for surgery for other reasons [55, 56]. A realistic patient selection will be biased on the drug resistant and inoperable cases. At the current state, neuromodulation techniques are considered as second-line "palliative" treatment, providing additional seizure-control in < 10% of the cases [57].

Important role of ongoing antiepileptic medication

The ongoing antiepileptic medication appears to play a specific role in degree of antiepileptic effects of tDCS and should therefore be controlled during stimulation protocols, or, if not possible, at least reported. Although the enrollment of patients without drug therapy would be the best solution to avoid confounding effects due to the AEDs, this is hardly feasible for ethical reasons, as a withdrawal of AEDs only for the study purpose could not be accepted.

An interesting research line investigated the behavior of neurotransmitters during tDCS, and in relation to this, the effect of concomitant antiepileptic drug treatment (AED). For example, the effects of both anodal and cathodal tDCS were prevented by blocking of glutamate receptors, whereas blocking of sodium and calcium channels inhibited the effects of anodal stimulation only [4, 58]. Moreover, the modulation of GABAergic interneurons was associated to excitatory anodal tDCS effects: the excitatory anodal stimulation effect was decreased by the simultaneous use of tDCS together with lorazepam, resulting in a diminished intracortical activation [59].

Reduced cortical GABA concentrations by decreased GABA synthesis could be demonstrated after the excitatory (anodal) tDCS, using MR spectroscopy, whereas inhibitory (cathodal) stimulation caused a reduction of excitatory glutamatergic neuronal activity [9].

Cathodal stimulation also prevented the normally occurring loss of GABAergic paired-pulse motor inhibition that usually provokes seizures in the context of pentylene-tetrazol use. This shows a further antiepileptic mechanism of cathodal tDCS [60]. The same study also observed a down-shift of EEG frequency spectral power in favor of low EEG frequencies after cathodal tDCS.

Therefore, in order to increase the antiepileptic stimulation effect, it might be suggested to combine cathodal tDCS together with anti-GABAergic AEDs, such as benzodiazepines (or valproic acid, felbamate, topiramate, and barbiturates). The sodium channel blocker carbamazepine selectively eliminated anodal effects by stabilizing the membrane potential voltage-dependently and inhibiting membrane depolarization [4, 58].

The role of localization of the epileptogenic focus

Because the direction of the electrical field influences the tDCS stimulation effect, the exact electrode montage on the head is a primordial factor in the stimulation protocol. The electrical field depends on the polarity of the electrode, as well as on the properties of the scalp and underlying tissue, and the possibility of current shunting by a transgyral or translobar short-cuts [61, 62]. Focality of tDCS is determined by the current density (mA/cm^2), as well as by the distance between the active electrode (over the area of interest) and the reference, and by their sizes.

A more precise and focal control of the current flow might be reached by a multi-electrode approach [63], or even a geodesic guided stimulation localization [64, 65]. However, with an increased focality of tDCS also localization precision of the epileptic focus needs improvement. This can be achieved when taking benefits from electrical high-resolution source localization (ESI) and allowing for in-depth target localization, especially when taking into account the patients individual anatomy [66 - 68].

On the other hand, the advantage of focalization is limited by the sometimes rather diffuse description at hand of the epileptogenic region or even network. The greatest success of neuromodulation is probably deep brain stimulation of the subthalamic nucleus (STN) in Parkinson's disease, which can be explained by the association of several factors: (1) the small size of the STN (< 1 cm), which is precisely localizable in MR scans; (2) the STN being a hub of the major cortico-basal loops; (3) the clear connectivity model of these loops explaining precisely clinical presentation. None of these conditions are given in epilepsy, being a symptom of different heterogeneous conditions covering different brain regions. The different etiologies (cortical dysplasia or brain lesion of variable size, non-lesional epilepsy, variable foci) require different approaches. Although epileptic activity has been shown to not only represent a local process, but is also abnormal neuronal activity

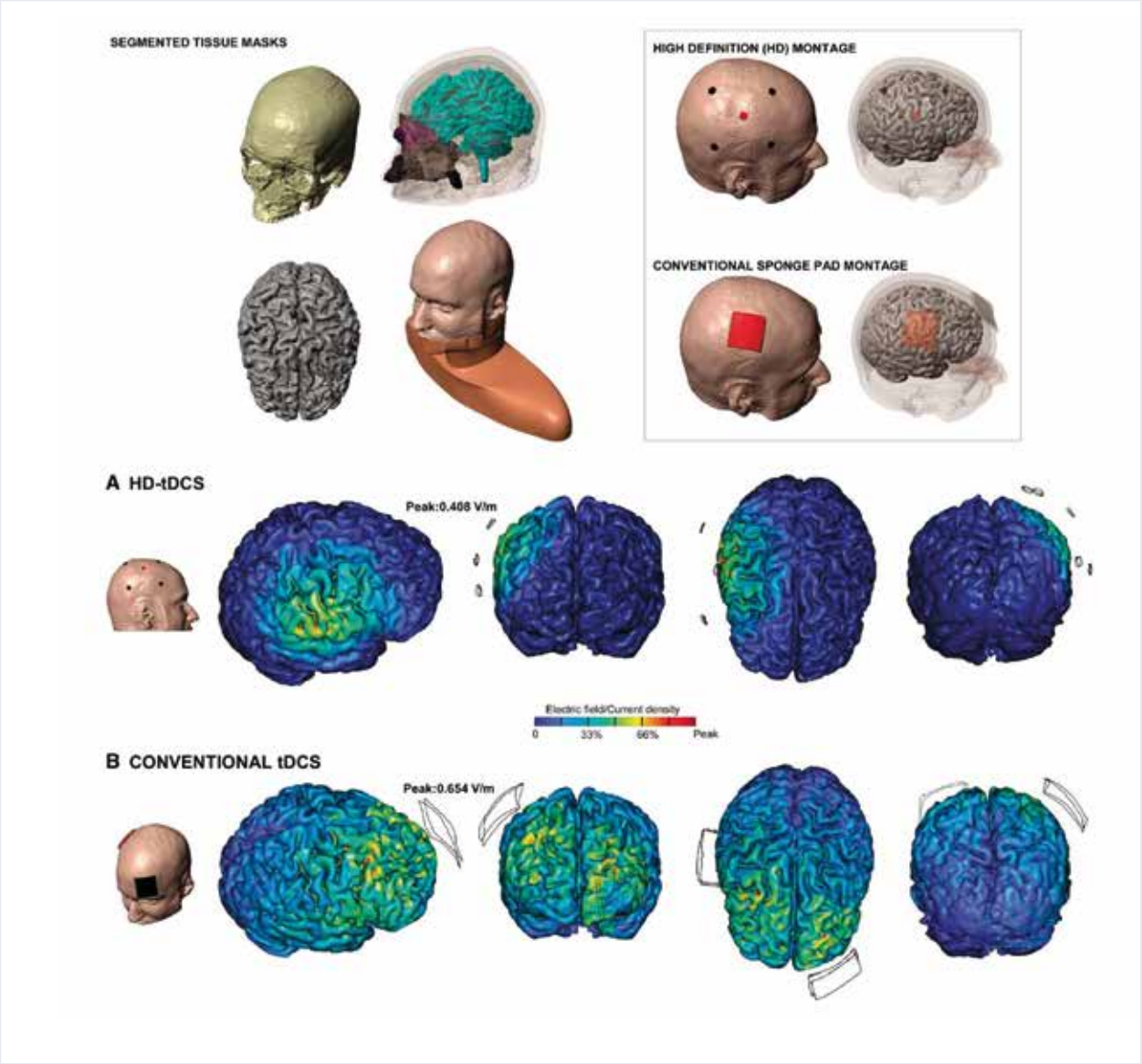

Figure 4. Simulation of the effects of high-definition tDCS (HD-tDCS), using a combination of dot shaped electrodes across the head, compared to conventional tDCS using a bipolar sponge montage. Top left: An individual anatomical head model is created using 4 - 8 tissue segments with different electrical properties. Boxed Right Panel: The distribution of anode and cathode in HD-tDCS (the anode, positioned over the motor region is surrounded by 4 cathodes), and conventional tDCS (anode centered over the motor region and cathode over the contralateral supraorbital region). A: HD-tDCS shows a restricted current flow compared to B: conventional tDCS where the current flow is largely diffuse (reprinted from [71] with permission of Elsevier).

in connected regions [69, 70], it is still very difficult to make use of these connections in order to stimulate the target area remotely. Moreover, the target areas are sometimes extending across several centimeters.

The evaluation of treatment success

Like for pharmacological studies, also in tDCS studies the evaluation of treatment success is based on seizure frequency and IEDs. To observe a significant decrease of seizure is a question of statistical power; for this result the patient needs to present a sufficient amount of seizures in a short time, and the observation period covered by the study needs to be long enough. Three studies couldn't find change of seizure frequency in the stimulation group compared to the sham group [45] or compared to baseline [36, 44]. Although, Liu et al. [44] had focused on patients with well-controlled TLE, in which no further improvement was actually to be expected.

However, San-Juan et al. used a 60-days observation period on a very homogeneously selected patient group with TLE, in which the monthly seizure frequency at baseline was median of 6 (range 3 - 30). In the group with 3-days stimulation, they observed a > 50% reduction of seizures in 50% of the patients, and in the group with 5-days stimulation even in 62.5% of the patients, however, the same effect was also observed in

25% of patients in the placebo group [42]. The study of Tektürk et al. found a similar result, i.e. a decrease of > 50% seizure frequency, in 10 out of 12 patients with TLE (83.33%), whereas 6 patients (50%) were even seizure-free during one month after stimulation. Nonetheless also here, a positive effect under the sham condition was found in two patients [43].

The effect of tDCS on IEDs is less clear. A significant reduction in IED was found only in one study, immediately after treatment, as well as persisting after 24 and after 48 h [40]. In another study, the focal decrease of 40 - 50%, was measured ipsilateral, but not on the contralateral side [37]. In the other studies it either did not reach significance [45], or no reduction of IEDs was found [36]. The most recent studies did not find any reduction, possibly due to infrequent IEDs at baseline [42, 44]. While interictal spikes are a marker of epileptic activity, their relationship to seizure frequency is not evident. On the other hand, the presence of IEDs in a routine EEG has been shown to be related to a two-fold higher risk of active epilepsy [72], suggesting therefore some prognostic information for clinical efficacy.

Conclusion

So far, tDCS has been investigated in a large spectrum of neurologic and psychiatric disorders in > 50.000 patients, with no reported complications at all. Concerning epilepsy a few studies have demonstrated seizure frequency reduction and IED decrease, however data are not sufficient to provide evidence of its antiepileptic efficacy. The currently most used stimulation protocol consists of a 20 - 40 minutes cathodal stimulation on three to five consecutive days. EEG is monitored before and after stimulation, as well as after one and after two months for long-term effects. When further evaluating tDCS in an antiepileptic purpose, larger studies are warranted across homogenous groups of patients. Very importantly, the ongoing antiepileptic medication plays an important role in tDCS effects and should be taken into account. Several new approaches have been developed to increase stimulation focality (high-definition-tDCS) which parallel the most recent algorithms allowing better localization of the epileptogenic focus (ESI), based on inverse solutions, and the patient's individual anatomy.

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