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EDITORIAL

Mechanisms of action of tDCS: A brief and practical overview

In this issue of Neurophysiologie Clinique/Clinical Neurophysiology (NCCN), Caeatano et al. showed that a 15-minute session of anodal or cathodal direct current stimulation does not lead to sustained excitability changes at axonal level beyond the period of stimulation [9]. This important result is an opportunity to reappraise the mechanisms of action of transcranial direct current stimulation (tDCS), which, among the techniques of low intensity transcranial electrical stimulation (tES) [3], currently has the strongest clinical development [23,26].

Historical overview of cranial electrical stimulation

Electrical stimulation delivered to the scalp includes varied approaches with very different mechanisms of action [21,22,27]. One form consists of superficial neurocutaneous stimulation and has its source in ancient Egypt (around 2000 BC) and the Roman Empire (Scribonius Largus, 43—48 BC) where patients were treated by placing a live electrical fish on their head. This method is the ancestor of supraorbital and transcutaneous occipital nerve stimulation. Then, in more modern times, ''peripheral'' electrotherapy was mainly developed for the rehabilitation of muscular paralysis. Following the pioneering work of Luigi Galvani, direct currents were used until Guillaume Duchenne (de Boulogne) showed in 1855 the value of pulsed alternating current and Wilhelm Erb structured the techniques of neuromuscular electrotherapy.

Concerning brain stimulation, electricity was first used in the second half of the 19th century for mapping and investigating cortical functions, leading to invasive stereotactic neurosurgical approaches through the work of Victor Horsley and Wilder Penfield among others. More recently, for diagnostic purposes in clinical neurophysiology, the value of high-voltage transcranial electrical stimulation (TES) in exciting the motor cortex was first reported in 1980 in England by Patrick Anthony Merton and H. B. Morton. Between these two periods, therapeutic application of electrical brain stimulation started in the 1930s in Italy with the work of Ugo Cerletti and Lucio Bini on electroconvulsive therapy (ECT) [34]. Later, other techniques, called cranial electrotherapy stimulation (CES) and based on various patterns of low intensity subconvulsive pulsating electrical stimulation were intensively studied, especially from the 1950s to the 1970s in Russia, including ''electrosleep'' therapy and ''electroanesthesia'' [18,29].

Another mode of brain stimulation is to use low intensity direct current stimulation (tDCS) in place of single or repeated brief electric shocks. The first report of therapeutic effect of low intensity galvanic current applied over the head was provided in 1804 by Giovanni Aldini, the nephew of Luigi Galvani, with a detailed description of a 27-year-old farmer who was completely relieved from melancholia after 6 weeks of stimulation [44]. In the 1960s and the 1970s, several clinical studies were conducted to use low intensity ($\leq$ 1 mA) direct current delivered for minutes or hours by an electrode placed on the scalp with an extracephalic ''return'' electrode, as a method of ''brain polarization'' to improve mood or alertness in psychiatric patients [31]. At that time, the tDCS approach was much less developed than CES techniques, although it was experimentally proven that the application of polarizing direct current to the cerebral cortex can modulate brain neural activity with significant after-effects [7]. Finally, the technique of tDCS reappeared in the clinical field with the publications of Alberto Priori and colleagues in Italy in 1998 [46] and Michael Nitsche and Walter Paulus in Germany in 2000 [39]. These studies confirmed in humans that tDCS was able to produce sustained excitability changes in the stimulated motor cortex. However, it is important to mention that in these two pioneering studies, the duration of the tDCS session was only 7 seconds [46] or ranged between 4 seconds and 5 minutes maximum

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[39]. These durations were much shorter than those used in subsequent studies (20—30 minutes), especially those with therapeutic purposes, as initiated from 2005—2006 with the work of Felipe Fregni [23]. Other historical aspects of tDCS are described elsewhere [15,60].

Mechanisms of action of tDCS: immediate versus after-effects

What are the mechanisms of action of tDCS? This is still an unresolved issue. As described below, the impact of subthreshold electric fields of very low magnitude on neurons and networks of neurons remains elusive. Results from long-term chronic stimulation together with large amounts of in vivo and in vitro data, suggest concurrent mechanisms of action. On one hand, acute effects result from membrane polarization [6] with a major downstream influence on neurotransmitter release [51], spike timing [50] and spike-timing-dependent plasticity [11]. On the other hand, short- and long-term therapeutic effects could be related to neurogenesis and cortical reorganization associated to synaptic plasticity, which is known to involve both stimulation intensity- and frequency-dependent processes [10,48].

Acute effects: polarization of axonal resting membrane potential

Regarding acute effects, it should be remembered that the current intensity delivered by tDCS (1—2 mA) is too low to directly elicit action potentials within the brain. Indeed, the peak electric field value is about 1 V/m (0.2—2 V/m or 0.05—0.5 A/m^2 current density) in response to tDCS delivered at 1—2 mA, which results in a membrane polarization change of 0.2 mV [19,36,52]. Such a tDCS-induced change in axonal membrane potential is insufficient for neurons to reach the threshold to initiate action potentials. This ''subthreshold'' property of tDCS contrasts with other techniques of brain stimulation such as transcranial magnetic stimulation (TMS), where the peak electric field value is about 100 V/m (Fig. 1a).

This difference partly explains why TMS and tDCS have a differential therapeutic effect, even when applied over the same cortical region in the same subjects [17].

Although debated [61], various in vivo measurements [43,53] have now provided evidence that the magnitude of the electric field produced by tDCS is sufficient to produce significant modulation of cortical network activity or excitability [33,63]. In fact, even though the impact of this electric field may be negligible at the level of individual neurons, the amplification provided by coupling mechanisms with local endogenous fields (referred to as ephaptic interactions [https://www.biorxiv.org/content/10.1101/688101v1]) and active ongoing firing of thousands of neurons, increases the strength of the tDCS to reach the threshold of potential efficiency at the network level [36]. By modulating axonal membrane potential, tDCS can interact with various endogenous neural network features, such as ion channel dynamics, spike timing, firing rate, oscillatory potential, synaptic transmission, and also brain responses to external stimuli [19,37].

Acute effects: influence of montage (anode versus cathode)

The most currently used montage of tDCS as a method of brain polarization is a bipolar montage, with a large anode and a large cathode, one of them being usually considered the active electrode and the other the ''return'' electrode, which can be placed in an extra-cephalic location [38]. However, other types of montage can be proposed in place of the classical bipolar montage. Firstly, some studies were performed with a ''high-definition'' Laplacian montage in which one central electrode is referenced to an average of four surrounding electrodes, in order to produce a more focal electric field. Secondly, a multifocal (multisite) montage can be used to more comprehensively and concomitantly modulate several brain networks. Multisite tDCS was found to be more powerful in modulating brain activity and excitability [12] but this approach requires detailed knowledge of functional brain connectivity in each individual, which can be provided by neuroimaging or electroencephalographic data.

In the case of a bipolar montage, the anode (positive red electrode) is thought to excite (depolarize) the underlying neural structure, whereas the cathode (negative black/blue electrode) is thought to produce the opposite effect (inhibitory hyperpolarization). This proposed dualistic neuromodulation is based on the ''somatic doctrine'' of tDCS [19]. Briefly, the anode is at the origin of an inward current flow (injection of cations) from the electrode to the brain, leading to hyperpolarize apical dendrites and then depolarize (excite) neuronal soma and axon hillock. Conversely, the cathode is at the origin of an outward current flow from the brain to the electrode, leading to depolarization of apical dendrites (accumulation of negative charges on the outer surface of the membrane) and then hyperpolarization (inhibition) of neuronal soma.

Acute effects: axonal modulation versus somatic doctrine

However, it has been shown that the axons are much more sensitive to electrical stimulation than the soma and dendrites according to their membrane properties (Fig. 1b) [41]. For example, the polarization of axon terminals by 1 mA tDCS is two to threefold greater than that of somas [36,50]. In fact, the preferential effects of electrical stimulation are observed on terminations of long and large axons, or at the level of axonal bending or collateral branching [57].

Actually, if tDCS acts preferentially on the axons, the effect of the polarity of the electrodes mainly depends on the orientation of these axons: cathodal stimulation tends to depolarize (excite) axons oriented parallel to the surface of the electrode and to inhibit perpendicular fibers (Fig. 1c) [32]. The reverse is observed for anodal stimulation, i.e. excitation of perpendicular fibers and inhibition of parallel fibers.

The fact that direct currents may act by two different ways, i.e. axonal modulation versus ''somatic doctrine'',

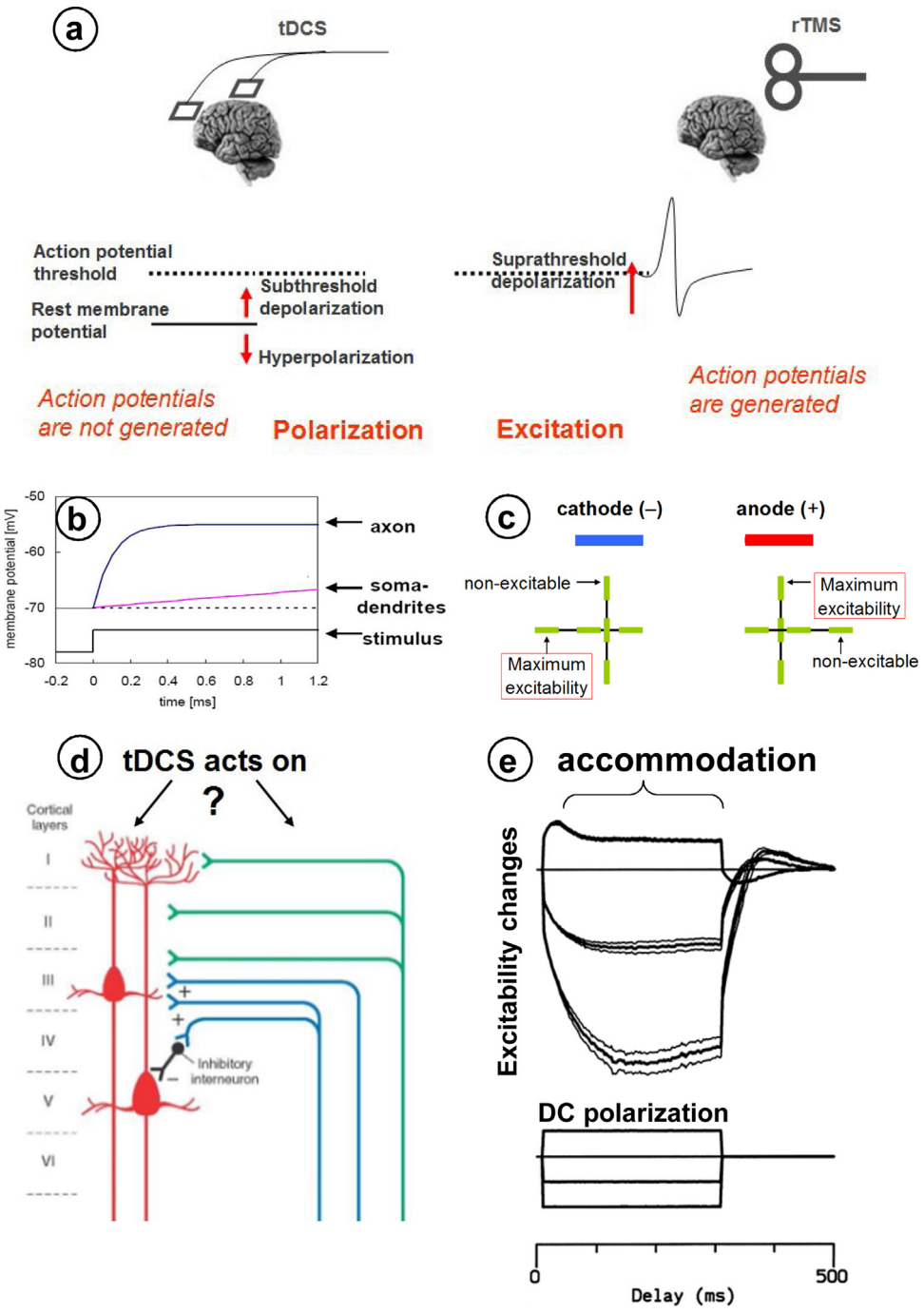

Figure 1 a. Transcranial direct current stimulation (tDCS) and repetitive transcranial magnetic stimulation (rTMS) have differential mechanisms of action with respect to the level of membrane potential changes and the ability to elicit action potentials. b. The changes in membrane potential induced by electrical stimulation are greater for axons than for soma and dendrites with respect to their membrane properties. c. The impact of the stimulation depends on the relationship between electrode polarity and the orientation of the axons, parallel or perpendicular to the electrode. d. It is not clear whether tDCS acts at somatodendritic or axonal level. e. There is a rapid accommodation of nerve fiber excitability to a prolonged depolarizing or hyperpolarizing current.

can explain the apparent discrepancy of some results. For example, a direct current delivered with a cathode increases neural excitability when applied over a peripheral motor nerve, whereas cortical excitability is decreased when cathodal tDCS is applied to the motor cortex [4]. On the one hand, increased nerve excitability may be due to depolarization of the axons running tangentially below the cathode (axonal modulation). On the other hand, decreased cortical excitability may be due to dendrite depolarization associated with soma hyperpolarization related to cathodal influence (''somatic doctrine'').

However, more complex mechanisms may be involved at cortical level. The ''somatic doctrine'' assumes that inward/outward current flows are purely radial to the electrodes and neglects tangential currents. Actually, tangential currents likely play a role in cerebral neuromodulation according to axonal orientation, which varies a lot with cortical folding (gyri/sulci).

Acute effects: conclusion

In conclusion, it is erroneous to consider that cathodal tDCS is purely ''inhibitory'' and anodal tDCS purely ''excitatory'', since it depends: (i) on where tDCS acts, i.e. the somatodendritic compartment, interneurons, or long axon endings (Fig. 1d); (ii) on the spatial orientation of these structures with respect to the electric field; (iii) on various modifying factors, such as those related to pathological conditions or medication. Therefore, anodal and cathodal tDCS may not have opposite biological effects for certain stimulation sites or pathologies. In any case, bipolar tDCS is able to modulate a variety of brain circuits at a distance from the site of stimulation, as shown by clinical and therapeutic studies in humans [13].

Influence of stimulation intensity and duration

One key variable to take into account for understanding tDCS effects is the stimulation intensity. In contrast to rTMS in which intensity is adjusted according to individual cortical excitability level (assessed by measuring the resting motor threshold), tDCS is usually delivered at a fixed intensity (1—2 mA) for all individuals. Increasing the stimulation intensity does not increase the effects but results in the neuromodulation of other circuits, and subsequently to potentially different clinical changes and therapeutic impact. For example, it has been shown that cathodal tDCS decreased M1 excitability when delivered at 1 mA, but increased M1 excitability when delivered at 2 mA, while such an increase was observed after anodal tDCS delivered at either 1 or 2 mA [5].

Another key variable in the effect of tDCS is the duration of the stimulation session [62]. It was shown that cortical neuromodulation requires a sufficient duration of stimulation time, both in experimental studies [33,55] and in clinical studies, at least for TMS [16]. Although tDCS induces a sustained depolarization/hyperpolarization, it is known that there is a strong, rapid (less than 100 ms), and physiological ''accommodation'' of nerve fiber excitability to a prolonged depolarizing or hyperpolarizing current (Fig. 1e). This axonal membrane property is used for assessing peripheral nerve excitability in threshold tracking techniques, such as a method called ''electrotonus'' [8]. Accommodation to depolarization involves nodal and internodal slow potassium channels (IKs current), while accommodation to hyperpolarization involves inward rectifier potassium channels (IH current). Accommodation can be altered in pathological conditions affecting potassium channels, as demonstrated in peripheral neuropathies [25].

After-effects: synaptic changes versus other mechanisms

Thus, immediate changes in neuronal network excitability are observed during a session of tDCS [30]. A totally different problem is to understand the short- or long-term changes that occur beyond the period of stimulation. In the aforementioned study of Caetano et al. [9], no lasting effect on local axonal excitability properties was observed in a series of 15 healthy subjects beyond a session of direct current stimulation applied to a peripheral nerve. Only one study previously addressed this issue [4] showing some changes in the stimulus-response curve after cathodal direct current stimulation delivered at 0.3 mA for 10 minutes over the ulnar nerve. However, this previous study was based on a smaller sample size (7 subjects) and a less reliable technique of nerve excitability testing than in the study of Caetano et al. [9]. Thus, there is still no convincing data that a non-synaptic modulation of neuronal excitability may support long-lasting after-effects of tDCS. The immediate effects of tDCS start with membrane polarization, but after-effects cannot be based solely and directly on such a mechanism [36].

Many therapeutic studies argue for the existence of prolonged after-effects occurring beyond tDCS sessions [23,26]. A variety of long-lasting events can be produced in the brain by the electric field resulting from tDCS application, including epigenetic regulation of neurotrophic factor expression, promotion of neurite growth, adaptive transduction affecting glial cells, or regulation of endothelial cells and blood-brain barrier permeability [19]. However, the main mechanism generally put forward is based on synaptic plasticity [45].

Indeed, it has been largely demonstrated that tDCS delivered to motor cortex could produce prolonged after-effects on its excitability assessed by various TMS variables [4,39,64,65]. These TMS variables mainly depend on the activity or excitability of GABAergic or glutamatergic circuits present in the motor cortex, and not on the intrinsic membrane properties of axonal excitability.

Since tDCS appears to have a preferential impact on axonal endings, it could favor plasticity at the presynaptic level [49]. A first hypothesis is that low-amplitude voltage gradients inducted by tDCS modify the spike timing of neurons [50] and therefore produce an alteration of spike-timing-dependent plasticity [11]. However, it has been shown that the weak polarization induced by tDCS was not sufficient to induced plastic changes at synaptic level in a neural network ''at rest'', without background ongoing activity [14]. Thus, a second hypothesis is that synaptic changes may require that tDCS impacts on concurrently active neural structures [14,33]. Consequently, long-term synaptic plasticity (either potentiation or depression) may relate to the combination of brain polarization induced by tDCS and endogenous synaptic input, favored by the mechanisms of coupling and amplification previously described for the immediate effects.

After-effects: influence of metaplasticity

Therefore, tDCS effects can be considered as the upstream modulation of afferents with top-down modulation of

synaptic transmission at the level of target structures, possibly at a distance from the location of the active electrode. However, the exact mechanisms by which the polarizing effect of tDCS interacts with these molecular changes at the origin of long-term synaptic potentiation or depression remain unknown. They potentially involve various neurotransmitter systems, such as glutamatergic transmission via NMDA receptors. This leads to protocols combining tDCS with pharmacological procedures [28,40], learning/training, or rehabilitation strategies [58,59] for priming the brain state to be more responsive to the stimulation. Such an approach is based on the concept of metaplasticity [1]. Indeed, synaptic plasticity depends on spike timing and synchronization arriving at the presynaptic level and the degree of postsynaptic activity. Whether a synapse is strengthened or weakened by presynaptic activity depends on the level of activity in the post-synaptic neuron. According to the Bienenstock—Cooper—Munro (BCM) model, depression of synaptic transmission is more effective when post-synaptic activity is high, and potentiation of synaptic transmission is more effective when post-synaptic activity is low. Priming protocols can modulate the initial state of cortical excitability, the functional connectivity between neural networks and the cooperation between synaptic inputs: they are therefore potentially able to largely influence the subsequent effects induced by tDCS.

Initial studies showed significant after-effects of brief sessions of tDCS delivered to the motor cortex [39,46]. It seems that polarity-dependent changes induced by tDCS in neuronal membrane potentials may lead to synaptically-driven after-effects only if the stimulation period is sufficiently prolonged or repeated [33,35]. For example, in a murine model of epilepsy, hippocampal paroxysmal discharges were reduced for at least 45 minutes after local direct current stimulation consisting of 50-sec periods of cathodal stimulation repeated every 5 minutes for one hour, showing a cumulative effect of the stimulation [35]. To our knowledge, such a protocol of brief and repeated stimulation periods has not been compared to a prolonged tDCS session with respect to its ability to promote functional or therapeutic changes in humans.

After-effects: therapeutic perspectives

The use of tDCS is now considered a therapeutic strategy that can be included in the therapeutic armamentarium of hospitals in clinical practice [54]. However, it is important to mention that tDCS can also be easily applied and self-addressed for long periods of time by the patients at home, as reported in various therapeutic reports or projects [2,20,42,47,56]. This is a positive point, although the fact that this technique is easy to use and inexpensive can be the cause of misuse, such as non-therapeutic applications of neuroenhancement [24].

In conclusion, real neuromodulation effects can be obtained with tDCS but there are many variables to control to optimize these effects, including the montage (bipolar, focal, multisite), the duration and repetition of the sessions (especially for at-home use), the intensity of stimulation (dose), or the possibility of combined strategies with a variety of priming procedures. To date, robust clinical results have been obtained with fairly simple protocols. However, the technical possibility of applying more sophisticated methods is crucial. Their therapeutic development will depend on the better understanding of the underlying mechanisms of action according to the methods used and the clinical indication. No ''general rule'' should be applied for a technique that lends itself remarkably well to an individualized approach tailored to each patient.

Disclosure of interest

The authors declare that they have no competing interest.

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