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Update article

Mechanisms underlying transcranial direct current stimulation in rehabilitation

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ABSTRACT

For a few years, the non-invasive modulation of motor cortex has become the centre of much attention because of its possible clinical impact. Among the different mechanism allowing to modify motor-cortex excitability, transcranial direct current stimulation (tDCS), with its efficacy and ease of use, plays a major role. The aim of this review is to improve the understanding of the underlying mechanisms of the tDCS effect in the field of rehabilitation. The mechanisms underlying tDCS effects when applied over the motor cortex differ depending on the polarity used. Moreover, the mechanisms underlying these effects differ during stimulation (per-stimulation) and after the end of it (after-effects). This review highlights the known mechanisms involved in tDCS effects on brain excitability and illustrates that most remain not well understood and debated. Further studies are necessary to elucidate the mode of action of tDCS and determine the best paradigm of stimulation depending on the goals.

1. Introduction

In the past few years, the non-invasive modulation of the motor cortex has generated much attention in light of its possible clinical impact. Among the different mechanisms allowing to modify motor-cortex excitability, 2 tools play a key role: repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS). With rTMS, the large rapidly changing magnetic field of a pulse induces an electrical stimulating current in the brain able to generate action potentials in the cortex and white matter. With tDCS, a portion of the long-lasting applied current enters the skull and modulates brain excitability without generating action potential.

However, the main mechanisms underlying the effects of the 2 tools differ. This article aims to improve our understanding of the underlying mechanisms of the tDCS effect in rehabilitation. We highlight the different mechanisms responsible for the effect observed during stimulation and after the end of stimulation (after-effects). This explanation will allow for a better understanding of why the tDCS effects are polarity-dependent. Finally, we show that these mechanisms remain partly unexplained and therefore further studies are required before this tool can be used in the clinic to decrease impairments in patients with central nervous system lesions.

2. Methodological point

We searched MEDLINE via PubMed with the following keywords: "transcranial direct current stimulation" and "mechanisms" and identified 274 references. However, when "rehabilitation" was associated with tDCS, the number of references increased to 352. Therefore, we limited our research to combining "tDCS" with "mechanism"; 45 references were chosen for their pertinence to this review.

3. Mechanisms underlying tDCS effects

Systematic investigations of the behavioural effects induced by direct current (DC) stimulation to the scalp in normal subjects date back at least 30 to 40 years. Using a very low scalp DC up to 50–500 μA in 32 healthy subjects, Lippold and Redfean (1964) found that scalp anodal currents increased alertness, mood and motor activity, whereas cathodal polarization produced quietness and apathy. DC passed through 2 frontal electrodes and 1 over the right knee [1]. Using a double-blind experimental design with objective methods for estimating mood and alertness in 6 healthy subjects,

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Scheffield and Mowbray (1968) failed to confirm the previous findings and concluded that scalp DC had no significant effect [2]. Similarly, Hall et al. (1970), studying 18 normal subjects with a double-blind experimental design, reported that currents up to 0.3 mA left the reaction time unchanged after an acoustic "go" signal [3]. More recently, in the late 1980s, Jaeger et al. observed that weak scalp DC (0.3 mA) affected the reaction time to an acoustic stimulus and the choice of the hand to push a button in response to an acoustic signal. These findings in normal subjects show that DC stimulation to the scalp may induce an important variety of excitability changes at the cortical level [4].

The first modern study demonstrating the modification of cortical excitability induced by tDCS was by Priori et al., in 1998 [5]. The authors tested the effects of tDCS on the excitability of the cerebral cortex using transcranial magnetic stimulation (TMS; a technique able to test cortical motor-area excitability directly), thus overcoming interpretative problems arising from previous phenomenological and descriptive studies. In 4 different experiments, they tested the functional effects of very weak DC stimulation (< 0.5 mA, duration < 7 s) on the motor areas of human cerebral cortex by studying changes in motor-evoked potential (MEP) elicited in small hand muscles in 15 healthy subjects. The authors placed the 2 electrodes over the skull and, with TMS, induced the motor response just before the end of the tDCS sequence. Anodal tDCS slightly but significantly and consistently reduced (by some 8%) the size of the controlled unconditioned motor response, whereas cathodal tDCS left the response unchanged. The authors also found that higher anodal DC stimulation produced progressively stronger depression of MEP. These findings provided the first direct evidence that a very small electrical field crosses the skull and affects brain excitability [5].

These initial findings were partially confirmed by the study of Nitsche and Paulus, in 2000, which is now considered the reference for tDCS (Fig. 1). In healthy subjects, the authors showed too that the modifications of the motor-cortex excitability induced by tDCS were polarity-dependent. They showed for the first time in humans, using a TMS approach to assess motor-cortex excitability, that anodal tDCS increases motor-cortex excitability, whereas cathodal tDCS decreases it. Indeed, anodal tDCS increased MEP amplitude by about 40%, whereas cathodal tDCS decreased it in the same range. The authors demonstrated that tDCS could modulate brain excitability and that:

- the best configuration to modify motor-cortex excitability was to place the active electrode in regards of the motor cortex and the other electrode on the contralateral supra orbital region;
- the effects of tDCS were present during stimulation and could last after the end of stimulation ("after-effects") (Fig. 2);
- the importance of the motor-cortex excitability changes depended on the intensity of stimulation;
- and at least 3 min of tDCS at 1 mA or an intensity of 0.6 mA for 5 min was necessary to induce after-effects [6].

Since this study, all the following studies that assessed the impact of tDCS on the motor cortex used the same design, with the same placement of electrode and duration of tDCS stimulation most of the time between 10 and 20 min at 1 to 2 mA. Since this time, this technique appears thus as a promising tool to modulate motor-cortex excitability and to induce either long-term potentiation or long-term depression.

The following studies tried to better define the main mechanisms underlying the polarity-dependent effects induced by tDCS. The results of these studies detailed as follows suggest that the mechanisms involved during stimulation differ from those during the after-effects.

3.1. Mechanisms underlying tDCS effects during stimulation

The effects of weak polarizing currents appear to critically depend on both the strength of the current applied and the duration of the application. DC stimulation is often described in terms of the charge density (C/cm^2), where 1 Coulomb (C) is the amount of the electric charge transported in 1 s by a steady current of 1 A.

Early studies in animals using direct cortical stimulation with a stimulus of 0.00013 to 0.3 C/cm^2 showed that if the anode was placed above the cortex, spontaneous neuronal activity was increased, whereas cathodal polarity resulted in reduced spontaneous discharges [7–9] due to sub-threshold changes in membrane polarisation [9]. However neurons throughout the cortex were not modulated in a homogenous manner. Neurons in deep cortical layers were often deactivated by anodal stimulation and activated by cathodal stimulation [9]. This finding would suggest that the orientation of neurons relative to the electrical fields is of vital importance to their response to stimulation. In addition, the

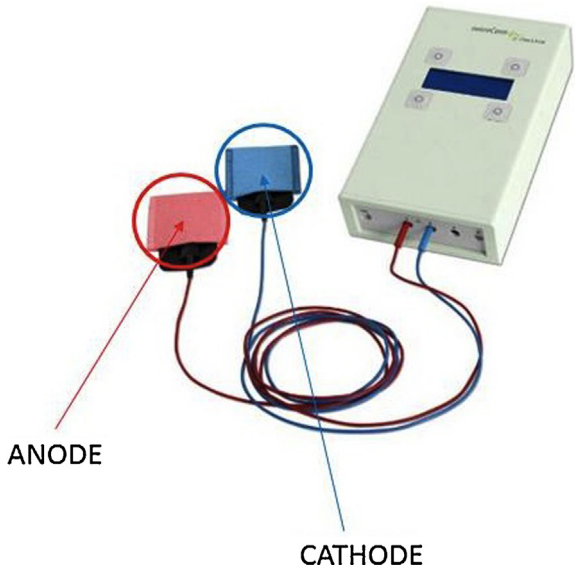

Fig. 1. Transcranial direct current stimulation device.

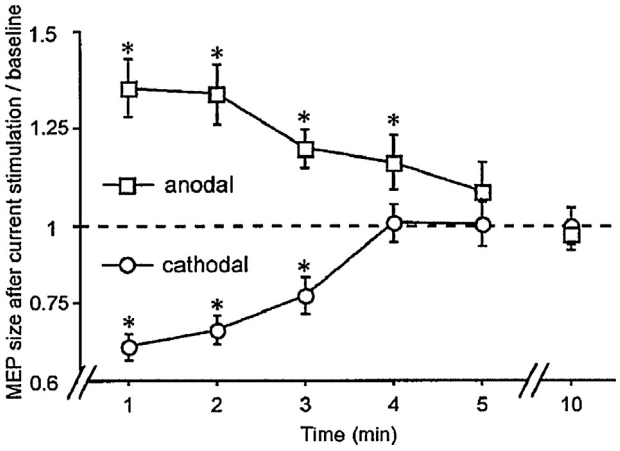

Fig. 2. Polarity-specific after-effects of direct current stimulation. Time course of polarity-specific motor-cortex excitability changes outlasting stimulation duration, shown after 5 min of direct current stimulation at 1 mA. MEP amplitudes returned to baseline within 5 min. Asterisks indicate significant differences between MEP amplitudes after stimulation and at baseline (two-tailed t test, paired samples, $P < 0.05$).
Figure from Nitsche and Paulus [6].

different subpopulations of neurons appear to have different thresholds of modulation. For example, non-pyramidal tract neurons were stimulated at lower total charges than pyramidal tract neurons, the activity of which was modulated only at charges $> 0.0008\ \mu C/cm^2$ [9]. These findings are important for human studies because they suggest that depending on the paradigm of stimulation used, tDCS is able to stimulate both pyramidal tract neurons and interneurons.

Results from humans suggest that the effects of tDCS during stimulation appear to depend solely on changes in membrane potentials. Indeed, Nitsche et al., using a pharmacological approach, found important results supporting this hypothesis. The authors assessed the impact of a sodium-channel blocker (carbamazepine) and a calcium-channel blocker (flunarizine) on tDCS-elicited motor cortical excitability changes in healthy human subjects [10]. Blocking voltage-dependent sodium channels completely eliminated the enhanced excitability observed during anodal tDCS and blocking the calcium channel diminished it. These results agreed with those observed in animals by Purpura and McMurtry, in 1965 [9], who also observed that reduced excitability induced by cathodal tDCS was not changed by ion channel blockade. Because the activity of both channels is voltage-dependent [11,12], this result could be due to cathodal tDCS-generated neuronal hyperpolarization, which in animals may represent the main mode of action of this type of tDCS stimulation [9]. This last result also indicates that further investigation is necessary to better understand the main mechanisms involved in the hyperpolarization induced by cathodal stimulation.

Moreover, concerning anodal stimulation, neither dextromorphane (antagonist of N-methyl-D-aspartate [NMDA] receptor) nor lorglumide (LOR; a gamma aminobutyric acid A [$GABA_A$] receptor agonist) had a modulatory effect on the per-stimulation response [10,13]. Anodal tDCS did not alter TMS measures of glutamatergic interneurons (absence of modification of intracortical facilitation) or gabarergic interneurons (absence of modification of short interval cortical inhibition). Thus, no significant modulation of the excitability of either glutamatergic or gabaergic internerneurons occurred during tDCS [13].

A recent publication by Bikson et al. suggested new types of reflexions to understand the other possible mechanisms induced by tDCS during stimulation [14]. Indeed these authors suggest that tDCS action could be more accurately described as redistributing polarization across the cellular axis, for example, one dendritic branch versus another [15,16]. This change in weight across the dendrite may provide a cellular substrate to affect the input bias of a network. The authors also suggested that polarization of the afferent axon itself appears to activate a specific pathway [16–19].

3.2. Mechanisms underlying tDCS after-effects

Concerning the possible mechanisms involved in the after-effects observed after tDCS sessions, a few hypotheses have been evoked.

With a pharmacological approach, the after-effects of anodal tDCS depend on membrane polarization. Indeed the administration of a calcium-or sodium-channel blocker abolished the after-effects of tDCS [10]. In addition, Liebantz et al. showed that dextromorphane (antagonist of NMDA receptor) prevented the induction of long-lasting after-effects induced by tDCS, whatever the polarity used. These results likely suggest that after-effects induced by tDCS rely on modification of NMDA-receptor sensitivity. Dopaminergic receptors participate in NMDA-receptor-dependent neuroplasticity [20]. Nitsche et al. showed that D2 receptor blockage by sulpiride abolished the induction of the after-effects by tDCS. This result supports the NMDA receptor playing a role in the after-effects observed after a tDCS session [21].

Another explanation relies on the modification of intracortical neurotransmitter concentrations. Indeed, Stagg et al., using magnetic resonance spectroscopy, assessed the polarity-sensitive modulation of cortical neurotransmitters induced by tDCS [22]. After anodal stimulation, the GABA concentration decreased significantly by $9.2 \pm 5.3\%$ relative to sham stimulation, with no change in glutamate concentration. In contrast, after cathodal tDCS, the glutamate concentration decreased by $19.1 \pm 5.3\%$ as compared with sham stimulation and the GABA concentration decreased by $11.1 \pm 6.8\%$. The reduction in GABA and glutamate concentrations was positively correlated. Therefore, the modification in NMDA-receptor sensitivity seems not the only mechanism responsible for the tDCS after-effects whatever the polarity used and the GABA neurotransmitter may play a key role in these tDCS-induced after-effects (Fig. 3).

These results also raise several questions. NMDA receptors are activated by glutamate, so the increase in NMDA-receptor sensitivity after anodal tDCS without modification of glutamate

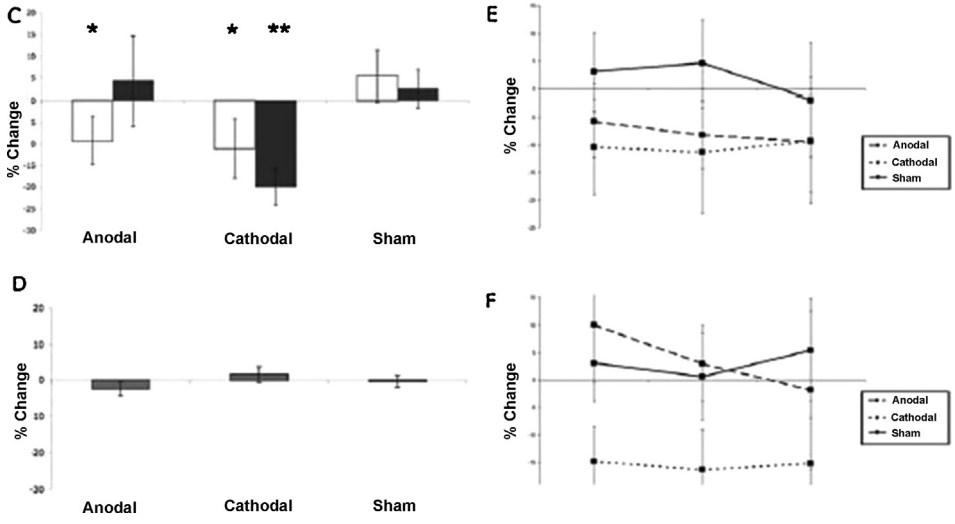

Fig. 3. C. Changes in neurotransmitter-to-naphthalene acetic acid (NAA) ratios, given as percentage change from baseline (mean ± SD). $^{*}P < 0.05$, $^{**}P < 0.01$. D. No change in absolute NAA quantification is seen in any stimulus condition. E and F. The decreases seen in both GABA (E) and Glx (the signal from unresolved glutamate and glutamine) (F) following stimulation were sustained over the 20-min scanning period.
Figure from Stagg et al. [22].

concentration might explain the long-term potentiation-like effects observed with anodal tDCS; this increased excitability could be favoured by the decrease in inhibitory GABA neurotransmitter concentration. After cathodal tDCS, the sensitivity of the NMDA receptor was suggested to be decreased, but because the concentration of glutamate also decreased, this result is difficult to conclude; in addition, this finding raises the question of the role of a concomitant decrease in cortical inhibitory GABA neurotransmitter concentrations.

A few other studies demonstrated that the plastic changes induced by tDCS involve regulation of a broad variety of other neurotransmitters, including dopamine, acetylcholine and serotonin [21,23,24]. The weak DC stimulation may induce several changes at different levels. Further studies are needed to better understand the different mechanisms supporting the tDCS after-effects and to optimize the after-effects in terms of the clinical objective.

A last mechanism was described by Ardolino et al. to explain the after-effects induced by tDCS. These authors showed that the after-effects of tDCS relied also on non-synaptic mechanisms of action based on changes in neuronal membrane function [17]; the after-effects could arise from alterations in transmembrane proteins and from electrolysis-related changes in $[H^+]$ induced by exposure to a constant electric field. This last result agrees with those obtained by Rae et al., who used magnetic resonance spectroscopy to show that before, during and after anodal tDCS, 2 biomechanical processes occurred with anodal tDCS: the first relied on a cellular consumption of adenosine triphosphate (ATP) causing hydrolysis of phosphocreatine via the creatine kinase reaction driving the increase in pH, and the second was based on synthesis of ATP and phospocreatinine by mitochondria with a concomitant decrease in inorganic phosphate and phosphomonoester levels [25].

4. Impact of tDCS on cortical connectivity

Polania et al. demonstrated that tDCS applied over M1 affects cortical connectivity, as measured by electroencephalography (EEG), with effects more evident when studying connectivity during hand movements than during rest [26,27]. Anodal tDCS over the left M1 with the cathode positioned over the contralateral supraorbital area increased synchronization in alpha and lower frequency bands in frontal and parieto-occipital regions and in the high gamma frequency (60–90 Hz) band in motor-related regions [26] during voluntary hand movements, with fewer changes during rest [26]. Another EEG study showed that tDCS over the left M1 during rest in healthy volunteers increased only the power density of low-frequency oscillation (theta, alpha) [28]. These results suggest that substantial changes in brain activity associated with tDCS are augmented when it is combined with performance in an active behavioural task, as predicted from basic science studies [15].

The effects of tDCS on functional connectivity have been studied with functional MRI (fMRI). Stagg et al. assessed the modulation of cerebral perfusion during and after tDCS applied to the left dorsolateral prefrontal cortex (Fig. 4) [22]. During stimulation, anodal tDCS increased the perfusion of the primary sensory motor cortex, midcingulate cortex, paracingulate cortex and left parietal cortex as compared with at baseline. As well, cathodal tDCS decreased perfusion in the thalami bilaterally and the right middle and inferior temporal gyri as compared with at baseline. Perfusion was higher with anodal than cathodal tDCS in the left stimulated dorsolateral prefrontal cortex and the paracingulate cortex. Perfusion was not higher in any regions with cathodal versus anodal tDCS. Concerning functional connectivity, during anodal tDCS, there was a coupling between the left dorsolateral prefrontal cortex and right dorsolateral prefrontal cortex and a decrease in coupling between the left dorsolateral prefrontal cortex and the thalami bilaterally, the brain stem and the cerebellum. During cathodal tDCS, coupling was significantly decreased between the left dorsolateral prefrontal cortex and an extensive region of the left temporal parietal and occipital lobes. Widespread perfusion was lower in the frontal lobes bilaterally, the cerebellum, and percuneus after anodal tDCS than during stimulation. Widespread perfusion was lower in occipital cortices and the cerebellum after cathodal tDCS than during tDCS.

So these authors demonstrated increased perfusion in regions closely anatomically connected to the dorsolateral prefrontal cortex during anodal tDCS combined with decreased functional

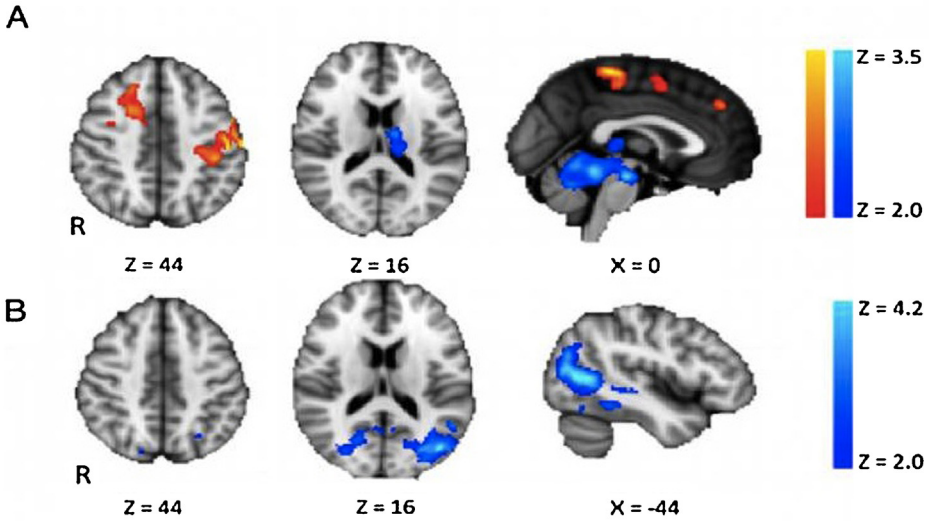

Fig. 4. Functional connectivity analysis from the stimulated left dorsolateral prefrontal cortex (L-DLPFC; $n = 12$; mixed effects, corrected cluster threshold, $Z > 2.0$, $P < 0.01$). A. Regions of altered functional connectivity during anodal stimulation [i.e. (anodal stimulation − anodal baseline)]. Significant increases in connectivity (in red/yellow) were seen between the L-DLPFC and the right DLPFC (R-DLPFC) and the left sensorimotor cortex. A significant decrease in connectivity (in blue) was seen between the L-DLPFC and the thalami bilaterally. B. Regions of decreased functional connectivity during cathodal stimulation [i.e. (cathodal stimulation − cathodal baseline)]. Decreased functional connectivity was observed between the L-DLPFC and an extensive region in the left temporal, parietal, and occipital lobes.
Figure from Stagg et al. [33].

coupling between the left dorsolateral prefrontal cortex and the thalami bilaterally. Despite highly similar effects on cortical excitability during and after stimulation, cortical perfusion changes markedly differed during these 2 time periods, with a widespread decrease in cortical perfusion demonstrated after both anodal and cathodal tDCS as compared with the period stimulation.

5. Impact of tDCS on spinal connectivity

Recently, Roche et al. demonstrated that anodal tDCS modified spinal-circuit excitability [29–32]. Indeed, anodal tDCS increased disynaptic inhibition directed from the extensor carpi radialis to the flexor carpi radialis during stimulation at the cervical spinal level [29,32]. The authors also showed that cathodal tDCS had no effect on all spinal circuits studied during stimulation and that neither anodal nor cathodal tDCS modified spinal-circuit excitability after the end of the stimulation; at the lumbar level, compared to sham stimulation, anodal tDCS during stimulation decreased lumbar propriospinal system excitability, reciprocal Ia inhibition directed from the tibialis anterior to soleus muscle and increased homonymous recurrent inhibition on soleus alpha motor neurons [28,29]. After the end of the anodal tDCS, the excitability of only one circuit was modified–the lumbar propriospinal system–which suggests that this is the only spinal circuit that can exhibit after-effects.

In regards with results obtained by Stagg et al. [22], these results indicate that the modifications of brain connectivity induced by anodal tDCS during stimulation can also induce changes of spinal-circuit excitability. However, the mechanisms underlying these changes and more particularly the descending pathway(s) involved need to be elucidated [33].

6. Perspectives

Special consideration should be given to the placement of the electrodes and the focality of the tDCS interventions. Newer tDCS montages include bipolar and monopolar scalp stimulation, the former consisting of both the cathode and anode placed on the scalp surface, and the latter consisting of the active electrode placed on the scalp with the reference placed on an extracephalic target (e.g., shoulder, leg, arm) [34]. Different electrode configurations may result in different patterns of current spreading over the scalp and consequently on the cortex; the typical "reference" position over the supraorbital region may reduce undesired stimulation in non-target regions, so newer monopolar stimulation montages attempt to avoid this problem [35]. In addition, high-resolution tDCS may improve the focality of this form of stimulation (high-definition tDCS: HD-tDCS) [36]. From an instrumental point of view, HD-tDCS uses multiple sites of anodal and cathodal stimulation to target a specific region. Despite substantial work under way to model the fields induces by these different montages, clear behavioural and physiological data are lacking on the difference between these approaches.

Another special consideration should be given to the current density used. Indeed most of the studies used a paradigm associating cortical stimulation at 1 or 2 mA during 10 to 20 min with a surface electrode of 25 or 35 cm^2. Recently, Bastani et al. used anodal tDCS to assess the differential modulation of corticospinal excitability induced by different current densities [37]. The authors studied the impact of 4 current intensities (0.3, 0.7, 1.4, 2 mA) resulting in current densities of 0.013, 0.029, 0.058 and 0.083 mA/cm^2, respectively, in 12 right-handed healthy subjects across different recording sessions. Anodal tDCS was applied continuously for 10 min with constant active and reference electrode sizes of 24 and 35 cm^2, respectively. The authors assessed cortical excitability before and during the 30 min after the end of the stimulation and found significant changes in corticospinal excitability as assessed by TMS between 0.013 and 0.029 mA/cm^2 but no difference between 0.013 and 0.058 or 0.083 mA/cm^2. Therefore, anodal tDCS with at 0.013 mA/cm^2 was the better setting to increase corticospinal excitability. This result suggests that further studies are required to better define the best paradigm for the use of anodal tDCS. As well, this paradigm, if as efficient as mentioned, would be better tolerated by patients and thus easier in clinical routine with a paradigm based on repetitive tDCS sessions.

At least in clinical practice, the use of tDCS to improve motor function has been assessed. Hummel et al. showed that repetitive tDCS sessions in stroke patients improved motor function [38]. However, concerning neuromodulation, the question still frequently debated is the following: To increase motor function, should the excitability of the damaged hemisphere be increased or the excitability of the intact hemisphere decreased? This question relies on the interhemispheric inhibition that exists between the damaged hemisphere and the "normal" one. In the motor domain, a commonly used setup consists, as mentioned above, of a unilateral anodal tDCS electrode over M1 controlateral to the moving learning or affected extremity, with the over electrode applied to the contralateral surpraorbital region. More recently, a new tDCS electrode arrangement involving simultaneous anodal tDCS of M1 and cathodal tDCS of the homologous M1 (bilateral tDCS) yielded more prominent behavioural effects in healthy subjects during a finger sequence task [39] and improved motor deficit in patients with chronic stroke [40]. The more powerful effects of bilateral tDCS over M1 was assumed to be related to a more pronounced interference with interhemispheric information processing as compared with unilateral tDCS over the M1 [39]. Shem et al. used fMRI to investigate changes in intrinsic functional connectivity elicited with both unilateral and bilateral tDCS over M1 during and after stimulation without any task engagement [41]. Uni- and bilateral tDCS over M1 resulted in functional connectivity changes in widespread brain areas as compared with sham stimulation both during and after stimulation. Bilateral tDCS predominately modulated changes in primary and secondary motor as well as prefrontal regions, whereas unilateral tDCS affected prefrontal, parietal and cerebellar areas. No direct effect was seen under the stimulating electrode in the unilateral condition. The time course in functional connectivity in the respective brain areas was non-linear and temporally dispersed. This result, as with previous results, suggest that the paradigm of tDCS stimulation should be clearly defined depending on the objective. Further studies are needed to define which, in clinical routine, is the best way of using tDCS to decrease impairments in patients.

7. Conclusion

This review highlights the known mechanisms involved in the effect of tDCS on brain excitability and illustrates that most of the mechanisms remain not well understood and debated. Further studies are needed to elucidate the mode of action of tDCS and determine the best paradigm of stimulation depending on the goals.

Because tDCS is a non-invasive, easy-to-use tool, this technique of neuromodulation seems bound to have an increasing role in medical management [42–44]. However, to define its optimal use, several points require further refinements: its use alone or in an occupational therapy session, the duration of the stimulation, the polarity and the intensity to use. Therefore, before this tool can be used routinely in rehabilitation centres, further randomised control trials are necessary.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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