The Effect of Transcranial Direct Current Stimulation (tDCS) Over Human Motor Function

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Abstract. Transcranial Direct Current Stimulation (tDCS) is a non-invasive, weak cortical neurostimulation technique which implements direct currents through two electrodes with opposite polarization when both are placed over a conductive surface (e.g. the scalp). It has demonstrated positive effects in a wide range of psychopathologies and neurological disorders in the last 15 years, being its neurophysiological modulatory effect on neuro-motor impairments one of the most important targets in tDCS researching. Thus, different motor-related pathologies have been improved by tDCS, such motor alterations after stroke, Parkinson's disease, cerebral palsy in childhood, multiple sclerosis, etc. The positive effects of tDCS on motor abilities, both pathological condition or in healthy population, define it as an interesting option to induce neurophysiological changes complementing the traditional rehabilitation procedures. The comprehension of its neurophysiological and biochemical effects, the development of more ideographic procedures, and its integration with pharmacological treatments are mandatory in order to further improve its usage in rehabilitation approaches.

1 Introduction

From ancient times, human being has tried to modulate the behavior and neural function by using electrical impulses directly on the Central Nervous System (CNS) [1]. The main goal was to "cure" or palliate neurological and psychiatric pathologies [2]. Instead, it was used for a better understanding of the brain physiology too [3]. Thus, the technological revolution and its integration in medical sciences in this past Century has let us going from lesser-controlled and dangerous tools to more efficient and safety stimulation devices, from paradigms of invasive deep stimulation (Deep Brain Stimulation), to non-invasive approaches as the Electro-convulsive therapy and transcranial electrostimulation techniques.

This last group represents the present and future of the main rehabilitation models, in both neurological and psychiatric alterations [4]. Thus, Transcranial Magnetic Stimulation (TMS) is the more-developed and researched methodology last decades.

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This tool generates rapid changes in the magnetic field in order to induce electrical currents through the brain, letting the specific modulation of the cortical excitability, both single-program and repetitive stimulation [5]. The use of TMS has demonstrated positive effects in multitude of pathologies [5, 6].

Meanwhile, another device has recently taken the world by storm in the neuroscience researching field, the transcranial Direct Current Stimulation (tDCS). This tool has made a revolution in the last 15 years in research, due to its better side effects, lesser cost, easier application and better management of control condition in experimental procedures than the methodologies described above [4]. Thus, the present chapter has the main goal of exploring the features and possibilities which tDCS offers as a present and future model for the rehabilitation of multitude of alterations which take place in the CNS, especially in pathologies with motor affectation.

2 What is tDCS?

tDCS is a non-invasive, weak cortical neurostimulation technique which implements a direct current though two electrodes with opposite polarization [7]. It is composed by one anode (positive pole) and one cathode (negative pole), both connected to a 9 volt battery, and covered by two conductive sponges soaked in saline [8]. When both electrodes are placed over a conductive surface (e.g. the scalp), a direct current from the anode to the cathode is generated, and triggers specific changes in cortical excitability in the tissue which is under the anode and the cathode. In research, the current intensity varies from 0.5 milliamps (mA) to 2 mA, with a variable time of application from 5 to 30 min directly over the scalp. Electrodes size is variable too, with a 4×4 (16 cm^2), 5×5 (25 cm^2), 5×7 (35 cm^2) and 6×6 (36 cm^2).

Both current intensity and electrode sizes are very important in order to know the current density, which is defined as the current intensity (expressed in amps -A-, mA and/or microamps -μA-), divided by the total surface volume which the electrode occupies, being expressed in research as $\mu A/cm^2$, mA/cm^2 and A/cm^2 [9], being the range from 0.028 to 0.06 mA/cm^2 the commonly used in research [10]. The electrode which is placed on the area of interest is called "active electrode", meanwhile the other one is called as the "reference electrode". In most of studies, the reference electrode has been placed over the contralateral orbit (just above the contralateral eye) [7], albeit it is usual its placement on neck, arms, chin, etc. Some recent studies have demonstrated that it is better considered to use a smaller active electrode [11–13].

2.1 Handicaps in the Current Density Distribution

One of the main handicaps that we find in the development of the stimulation is the high current density which is concentrated in the edges of the electrode. This is undesirable for safety considerations and it can raise the aversive sensation during the transcutaneous stimulation. Indeed, various authors have defined and tested the current technique protocols by the development of circular electrodes instead of square-shaped ones [14]. This has to be added to the importance of the control of the saline quantity which is

incorporated to both sponges, which main function is to facilitate the electric current transmission [14], and the consideration of the "Shunting effect", which is defined as the important amount of electric charge which is lost by the effect of the skin (maximum skin current density), the skull and the cerebrospinal liquid [15]. Current research is focused too in the spatial distribution of the electrodes and how it can facilitate the "Shunting effect" in order to avoid it [13].

2.2 Place of Stimulation and Focality

The emplacement of both electrodes is essential in order to develop an efficient stimulation. Neuroimaging and neurophysiological studies confirmed that polarizing effects of tDCS under the electrodes [16, 17]. The specific stimulation of primary motor cortex (M1), primary visual cortex (V1), somatosensory cortex and areas of frontal lobe has reaffirmed this conclusion, defending the focality and specificity of the stimulation with tDCS over the scalp [24], above all when electrodes size is reduced and the inter-electrode distance is controlled [13].

Nevertheless, recent studies with functional Magnetic Resonance (fMRI) and positron emission tomography (PET) have demonstrated that, despite of the fact that tDCS has its largest effects under the electrodes [18], the stimulation generates sustained and generalized effects in other areas of the CNS [19]. These data can be added to studies with electroencephalography (EEG), which have shown that through the modulation of certain areas by cathodic stimulation, diffused effects throughout the CNS can be observed [20]. Thus, these evidences suggest that the effects of stimulation with tDCS are temporal and spatially specific, but not limited to a single place (site specific but not site limited [10]). That is to say, the stimulation of one area will probably affect others throughout neural circuit networks [21]. This is not surprising due to the complex anatomy and function of the human CNS, but it forces to make an exhaustive analysis of the stimulated area and its relationship with closer structures, it does not matter cortical or subcortical in nature [22, 23].

3 Neurophisiology of tDCS: General Concepts

The specific effects of tDCS into the CNS are still unknown. Nevertheless, it is widely confirmed that its general effect is a modulation of the resting membrane potentials of the cortical neurons which are placed under the electrodes. An increment or decrease of the cortical excitability can be observed depending on the direction and the current intensity applied [24]. After the stimulation, the main effects duration of a single 10 min session can go further 90 min [25]. These changes depend on the polarity of the stimulation, differentiating between anodal and cathodic stimulation.

The area which is directly stimulated by the anode shows a depolarization of the resting membrane potential, which raises the neuronal excitability up and lets a faster and more spontaneous response of the neurons under the electrode. When the area is stimulated by the cathode, the direct current causes a hyperpolarization of the resting potential of the membrane, dropping down the excitability of the neurons under the electrode [7].

3.1 Neurophysiology of tDCS: What Do We Know?

Ardolino et al. [20] observed that short-term tDCS effects are due to local changes in ionic concentrations, specific alterations in transmembrane proteins and to electrolysis related with subtle changes in the Hydrogen protons concentration. As we mentioned above, the mechanisms are not clear, but the tDCS action seems to be related with a hyperpolarization and depolarization combination in the membranes of the neurons, as well as certain alterations in the synaptic efficiency [26, 27]. Following this idea, recent studies have observed a large accumulation of myoinositol into the phospholipid membrane after atDCS on the right frontal lobe by a proton magnetic resonance spectroscopy [28] and a high increase of oxyhemoglobin concentrations after 1 mA of atDCS by a near-infrared spectography [29].

Despite the large number of works which have elucidated many physiological aspects underlying the tDCS effects, it still does not exist a potent theoretical model which explains all its features. Anyway, some authors as Molaee-Ardekani et al., [30] have recently developed a mesoscopic model (the study of population of neurons) over the somatosensory cortex in order to generate a basic structure to explain tDCS effects. Thus, they proposed that the transformation of the presynaptic pulse density of the afferent action potentials into modulated potentials in postsynaptic membrane drives to sustained changes in the local field potentials, and this changes the neural firing rates at different neural sub-population levels (Pyramidal cells, types I and I' Interneurons cells).

As these authors pointed out, the main effects of tDCS seem to be focused in pyramidal cells in the cortex. At the same time, different neuronal groups play the role of facilitating/inhibiting the electric impulse propagation and, thus, are critical in the generation of the evoked potentials (EPs). This neuronal set is composed by Interneurons, whose ortodromic direction (soma/dendrite axe) will facilitate (alignment with stimulation direction) or difficult (non-alignment with stimulation direction) the change in transmembrane potential, as well as happens with pyramidal cells (more information in Molanee-Ardekani et al., [30]). Thus, atDCS seems to be implicated in the selective depolarization of Pyramidal cells and type I interneurons, meanwhile ctDCS hyperpolarizes such cells, showing the opposite effect. Such model could explain short-term plasticity following tDCS [31].

This pyramidal cells/interneurons interaction is regulated by the excitatory mechanisms, guided by the action of the glutamatergic system, and the inhibitory action is controlled, eminently, by gamma-Aminobutyric acid (GABA) tone (Neural mass type model). Therefore, different factors like intensity and density of stimulation, and soma-dendrite axe orientation are essential for the final EPs generation after tDCS intervention. These, finally, will have repercussions in the selective modulation of the spatial and functional conformation of the dendritic ramifications at cortex level, altering their shape/orientation, as well as the total number of functional synapses which they can develop. This phenomenon of dendritic modulation, added to the later phosphorylation of proteins and transcription factors in the cellular nucleus, represents a process very similar to long-term potentiaton [32] and depression, bases of long-term cerebral plasticity [24].

3.2 Biochemistry of tDCS

Many studies have demonstrated substantial neurochemical differences between both types of stimulation (anodal and cathodic). Researchers have agreed that the excitatory effects of atDCS are mediated, at least in part, by an important reduction of the GABAergic activity and a facilitation of the glutamatergic N-methyl-D-aspartate receptors (NMDAr) [16, 33].

Otherwise, the inhibitory effects of the cathodic tDCS (ctDCS) seem to be mediated by an important reduction of the glutamatergic excitatory system [34]. It has been also observed a correlation between the increase of the monoaminergic tone and a strongest facilitation of the neuroplastic changes induced by the tDCS [35]. Such neuroplastic phenomena can be facilitated by certain pharmacological compounds like Citalopram (selective serotonin reuptake inhibitor) [36]. More recently, tDCS has been linked with adenosine A1 receptor [37, 38].

Finally, pharmacological studies have demonstrated that the tDCS effects, both immediate and long-term ones, can be eliminated by the selective blockade of Sodium (carbamazepine) and Calcium (flunarizine) channels, as well those long-term effects can be disturbed by the blockade of NMDAr (dextromethorphane) [16]. Added to this, the administration of L-Dopa [39] can turn into inhibition those neuroplastic effects after atDCS application and enhance inhibitory influence of ctDCS.

4 Safety Considerations for tDCS

Many studies corroborate that tDCS is a safety and suitable-for-use methodology in humans, and that it is linked to adverse effects only in rare occasions [40]. As well as in its clinical/experimental usage, variables, which we have to consider for safety concerns, are: current intensity, electrode size, current density, total stimulation time and number of sessions [41–43].

Iyer et al. [42] did not observed any sort of side effects, neither in cognitive nor psychomotor measures after 20 min of stimulation, both anodal and cathodic, and both current intensity of 1 mA and 2 mA in the prefrontal cortex. Added to this, indirect biomarkers of brain damage have demonstrated that tDCS application does increase neither the serum levels of the molecular markers of neuronal lesion (N-acetil-aspartate), nor the specific neuronal Enolasa [28]. Thus, no pathological changes by fMRI and EEG have been related to the application of tDCS [17, 42]. Outer the CNS, researchers have focused in the tDCS effects on the heart function, being minimal and non-harmful at any grade in this organ [44].

An exhaustive analysis conducted by Poreisz et al. [40] demonstrated that, after 567 tDCS sessions (both cathodic and anodal) in 102 subjects (both healthy subjects and with diverse neuropathologies patients), no significant negative effects were observed. The stimulation process, with a mean of 12 min, a current intensity of 1 mA, and a reference electrode size of 35 cm^2, showed better side effects than previous researches which used TMS.

Despite of the fact that tDCS is a widely known safety tool, is not free of side effects. The more common observed side effects are: subtle tingle, moderate fatigue, soft itching

sensations, mild burning and slight pain just under the electrodes [40]. Less common, head ache, difficulty to concentration, nausea and sleep disturbances [40]. In rare occasions, skin lesions by burns after the stimulation have been produced [45]. Anyway, this last phenomenon is related to the electrode shapes used at early stages of the use of tDCS in science, and some researchers argue that it is very important to discern the independence between side skin effects and its null repercussion in the cerebral tissue [15]. No convulsive effects have been linked to tDCS application by now [46].

5 tDCS on Motor Function in Patients with Motor-Related Pathologies

5.1 Stroke and tDCS

Motor recovery after stroke is linked to the maintenance of ipsilesional motor networks and interactions between ipsilateral and contralesional hemispheres [47], and the tDCS application seems to be capable to modulate them in post-stroke patients. Schlaug et al. [48] defended a hypothetic inter-hemispheric inhibition model by comparing the use of atDCS on the lessoned hemispheric and the cathode in the preserved one, demonstrating that larger effects can be observed by the cathodic stimulation of non-affected hemisphere, presumably due to the current density distribution is not disturbed by a lesion, with intact intracortical networks.

Following this line, Lidenberg et al. [47] showed that, by combining the stimulation on both hemispheres (atDCS on ipsilateral M1 and ctDCS on contralesional M1), 1.5 mA (0.09 mA/cm^2) during 30 min, added to orthodox occupancy and physical therapy (OT/PT), motor functions of post-stroke patients were improved stronger than those which receive OT/PT and Sham stimulation. Nevertheless, not all the studies have found this superiority of bilateral approach over single anodal/cathodal interventions [49], with 20 min of tDCS by 1 mA (0.029 mA/cm^2), showing strongest behavioral and physiological (Motor evoked potentials -MEPs-) changes at single interventions.

Otherwise, a significant improvement assessed in a specific hand function task for daily living activities (Jebsen-Taylor hand function test) was observed after the application of 1 mA (0.04 mA/cm^2) of atDCS during 20 min on post-stroke patients' M1 [50], but not with sham stimulation, resulting in functional gains in motor function of the paretic hand. This ipsilesional stimulation has been successfully confirmed in acute interventions too, when stroke is recent [51], showing significant improvements further to 15 days after the stimulation.

Such unilateral tDCS positive effects have been demonstrated further over hand function after stroke. Indeed, post-stroke aphasia has been selected as a key target for tDCS intervention. Rosso et al. [52] demonstrated that, after the application of 1 mA (0.028 mA/cm^2) of ctDCS during 15 min over the right Broca's area, improved language performance was developed, defending the idea that ctDCS can suppress inhibitory inter-hemispheric influences from the right Broca's area to the affected one, and that inter-individual differences are key in order to design accurately stimulation procedures. Those effects could be mediated by GABAergic intracortical and inter-hemispheric function [53].

5.2 Dysphagia and tDCS

Dysphagia is a high disrupting possible post-stroke effect. It consists on the impossibility of the patient to start and accomplish the voluntary or involuntary behavior of swallowing. This issue causes serious consequences as nutritional problems; complications of pulmonary aspiration and daily life deficits for the impossibility of swallow even saliva [54, 55].

It is well known that the primary motor cortex plays the principal role on the voluntary activation of the swallowing behavior, appearing both hemispheres to be responsible for this process [56]. However, neuroimaging techniques showed that in the majority of individuals, the projection during swallowing was larger in one hemisphere than in other, being this fact independent of handedness and showing to be different between a pair of identical right-handed twins. Besides the primary motor cortex, it is important to highlight that also the insula, predominantly on the right side, and the cerebellum, mainly on the left side, are also recruited by the swallowing mechanism [57]. Therefore, various areas are involved on the development of this complex mechanism, but, at any rate, the primarily motor cortex is a key target area for the use of tDCS stimulation as a treatment for dysphagia.

Studies related to this possibility have been performed across the last years with positive effects over post-stroke dysphagia patients (for review, see Sandrini & Cohen [58]). For instance, in the study of Kumar et al. [59] tDCS or sham on the motor cortex was applied in conjunction with standardized swallowing maneuvers. Anodal or sham tDCS with 2 mA for 30 min were administered over the undamaged hemisphere during 5 consecutive days providing a significant improvement of the scores obtained in the Dysphagia Outcome and Severity Scale (DOSS). Also Yang et al. [60] showed a positive effect of anodal tDCS, 1 mA, for 20 min during 10 consecutive days during swallowing training over the pharyngeal motor cortex of the affected hemisphere. Measures were taken by the Functional dysphagia scale (FDS) using the video fluoroscopic swallowing (VFSS) immediately after the intervention and three months later. Both, the anodal and the sham condition group improved their scores immediately after the intervention equally. However, the differences between the groups emerged on the second evaluation, scoring the anodal stimulated patients significantly higher three months later.

5.3 Parkinson's Disease and tDCS

Broeder et al. [61] have recently made an exhaustive review of the main behavioral and physiological effects of tDCS application in patients with Parkinson's disease. Despite of the importance of cognitive alterations, we will only focus on motor-type ones. Thus, Fregni et al. [62] demonstrated that, after only one session of atDCS on left M1 in patients in OFF-phase, with a current density of 0.029 mA/cm^2 (1 mA, 35 cm^2) for 20 min, a significant increase in MEPs amplitude were produced compared to sham condition, with a clear decrease of MEPs amplitude after ctDCS. All these results correlated with motor improvements as well (tremor, bradykinesia, rigidity, postural instability, gait, etc.). Other studies, which implemented 5 consecutive days of atDCS, 2 mA (0.057 mA/cm^2) have supported these results in patients in ON-phase [63]. Specific motor positive effects have been observed on gait and upper limb performance too [64].

Following this motor improvement, an original single-case study by Kaksi et al. [65] demonstrated that, after the application of atDCS, with a current intensity of 2 mA (0.05 mA/cm^2), over both superior M1 and preMotor cortices (Cz position in 10-20 EEG System), a significant improvement during a tango dancing in trunk and lower extremity movements was produced. This complements the general improvements in upper limbs widely demonstrated by other authors.

Finally, a study conducted by Pereira et al. [66] showed specific linguistic and physiological modulations in the CNS after atDCS, with a current intensity of 2 mA (0.057 mA/cm^2), during 20 min on both the left dorsolateral prefrontal cortex (DLPFC) and left temporo-parietal cortex (TPC). Phonemic fluency enhancements were observed in patients with Parkinson's disease after the stimulation of left DLPFC, but not after the stimulation on TPC, by increasing the connectivity of verbal fluency networks involving frontal, parietal and fusiform areas, changes quite larger in phonemic fluency than semantic, representing a clear proof of the widely known dissociation between both functions into the CNS.

5.4 Spinal Cord Injury and tDCS

After the widely known (but limited) effects of tDCS and TMS on the management of neuropathic pain after spinal cord injury [67], motor-related effects have been converted as a key target in researching. Thus, Silva et al. [68] demonstrated that, after the application of atDCS on both M1 (Cz position in EEG 10-20 system) with a current intensity of 2 mA (0.057 mA/cm^2) for 12 min in a male with total chronic spinal cord injury, a general improvement in exercise tolerance was observed by measuring specific changes in exercise time and power, perceived exertion, glucose levels, and variability of the time needed to reach the threshold of heart rate.

Otherwise, Murray et al. [69] demonstrated that, after the stimulation by atDCS on left M1 (extensor carpi radialis muscle representation) of 9 patients with chronic spinal cord injury, with a current intensity of 2 mA (0.64 mA/cm^2) for 20 min, three sessions in 3 weeks, an important increase (up to 40 %) in corticospinal excitability (MEPs) amplitude was observed. This did not happen with 1 mA stimulation procedure. Instead of the high current density implemented by the authors, no significant side effects were observed.

Nevertheless, the strongest positive tDCS effects in this pathologic population have not been reached by traditional cortex stimulation approach. Transcutaneous spinal direct current stimulation (tsDCS) represents a novel practice where the active electrode is placed over the back. Thus, Hubli et al. [70] placed the active electrode longitudinally between the spinous processes of T11 and T12, with a current intensity of 2.5 mA (0.056 mA/cm^2) for 20 min, both cathodal and anodal stimulation and both patients with spinal cord injury and healthy subjects. That procedure showed specific differences in spinal reflex behavior between pathologic and healthy subjects, where patients showed higher changes in spinal reflex amplitude after atsDCS, being even better modulation than a single session of assisted walking in the driven gait orthosis "Lokomat".

Also, changes in conduction along lemniscal pathway (specific somatosensory evoked potentials amplitude P30) in healthy subjects after the application of atsDCS over the spinous process of the T10 have been observed, with a current intensity of 2.5 mA (0.071 mA/cm^2) during 15 min [71].

5.5 Cerebral Palsy in Children and tDCS

Cerebral palsy refers to permanent, mutable motor development disorders stemming from a primary brain lesion, causing secondary musculoskeletal problems and limitations in activities of daily living [72]. This disease is the most common motor disorder in children [73].

As we will see, there are several studies of tDCS involving children suggesting the safety of this method. However, it is showed that lesser intensity is required than that used normally on adults to produce cortex stimulation on children, as the peak electrical fields for a given stimulus intensity in the adolescent brain were twice as high as in the adult brain for conventional tDCS [74].

Recently, some studies have found positive effect of tDCS on cerebral palsy when combined with training and rehabilitation. On a study with 24 children with cerebral palsy, positive effects of tDCS combined with treadmill training were observed on balance and functional performance. 1 mA anodal tDCS was administered over 5 weekly sessions of 20 min during 2 weeks over the primary motor cortex of the non-dominant hemisphere during the performance of the treadmill training. The evaluation was carried out with the Pediatric Balance Scale (PBS) and the Pediatric Evaluation of Disability Inventory (PEDI) finding positive effects on the experimental group on balance one week and one month after the treatment, however, no positive effects were found on the self-care and mobility PBS subscales [72].

Spasticity, which is one of the most common symptoms of cerebral palsy [75], is an upper motor neuron syndrome characterized by a velocity-dependent increase in the tonic stretch reflexes with exaggerated tendon jerks resulting from hyperexcitability of this reflex [76]. In a recent study carried out by Aree-uea et al. [77] 46 children between 8 and 18 years with cerebral palsy were tested on spasticity before and after a 1-mA anodal tDCS treatment over the left primary motor cortex during 5 consecutive sessions combined with physical stretching exercises. Results showed a reduction of finger spasticity immediately after the treatment, a reduction of the elbow spasticity immediately and 24 after the treatment and a reduction of wrist spasticity immediately, 24 and 48 h after the treatment. However, no effects of tDCS were found regarding elbow spasticity.

tDCS combined with virtual reality training has also shown to produce positive effects on the body sway velocity [78], as well as regarding spatiotemporal gait variables (velocity and cadence), gross motor function and mobility [79]. Furthermore, in this last study anodal tDCS led to a significant change in motor cortex plasticity, as evidenced by the increase in the amplitude of the motor evoked potential.

Therefore, accompanied with motor training and using specific parameters, tDCS might be a promising technique to improve the symptoms of cerebral palsy in children.

5.6 Multiple Sclerosis/Amyotrophic Lateral Sclerosis and tDCS

Few studies from 2010 have focused on different motor and cognitive effects of the application of tDCS in patients with multiple sclerosis [80]. Thus, Cuypers et al. [81] demonstrated that, after the application of atDCS with a current intensity of 1 mA (0.04 mA/cm^2) for 20 min on M1 (First Dorsal Interosseous), contralateral to the more impaired hand, a significant corticospinal excitability increase was observed evaluated by MEP variations, effect non-observed after sham stimulation. This cortical modulation triggered to a recruitment-curve plateau increase, something which could be explained by distal effects mediated by large-diameter myelinated axons. Nevertheless, no functional effects were studied. However, no motor improvement facilitation were observed by Meesen et al. [82] after atDCS with a current intensity of 1 mA (0.04 mA/cm^2) for 20 min on contralateral to impaired hand M1, compared to sham condition. Further researches in motor function are needed.

Otherwise, and due to the lack of motor assessment studies, positive sensory modulations have been observed after atDCS application in patients with multiple sclerosis [80]. Mori et al. [83] demonstrated that, by applying atDCS with a current intensity of 2 mA (0.057 mA/cm^2), during 20 min/5 consecutive daily stimulation on somatosensory cortex (S1), temporally ameliorated sensory deficits (spatial discrimination thresholds on the hypoesthetic hand) further to 2 weeks after treatment were observed in patients with multiple sclerosis. These sorts of positive sensory modulations have been observed too in pain self-sensation in patients with multiple sclerosis [84], after the application of atDCS with a current intensity of 2 mA (0.057 mA/cm^2), during 20 min/5 consecutive daily stimulation on contralateral to somatic painful area M1, with a clear decreasement of values in standarized pain scales.

On the other hand, little use of tDCS has been developed on Amyotrophic lateral sclerosis (ALS). As Di Lazzaro et al. [85] pointed out, after the variable results of the application of TMS in patients with ALS, tDCS could be considered as a better intervention tool due to its longer-lasting effects on cortical excitability. Thus, and as a preliminal study, these authors showed no significant effects after ctDCS on M1 (the cortical representation of the first dorsal interosseous muscle), with a current intensity of 1 mA (0.029 mA/cm^2) for 20 min on both hemispheres in two different patients. Related to this, Munneke et al. [86] demonstrated no significant cortical excitability variations after 1 mA ctDCS during 7, 11 and 15 min. However, an important effect was observed in healthy subjects, indicating that patients with ALS could have less responsive corticospinal pathways to the inhibitory ctDCS effects. Such results were early demonstrated by Quartarone et al. [87] in both anodal and cathodic stimulation types. Nevertheless, it has been demonstrated that continuous theta burst stimulation (cTBS) by TMS can induce an inhibitory effect on corticospinal excitability in patients with ALS only after 5 daily sessions [88], so it is not unreasonable to postulate that repetitive ctDCS training could generate similar effects on patients with ALS.

6 Conclusions

TDCS is a stimulation device whose neuromodulation properties have been widely demonstrated last decade. At the same time, its soft side effects, easy administration, good sham condition control and low price are essential keys in order to understand the reason why hundred of researches are focusing on its study [26].

The large ranges of variants for usage of tDCS are vast, due to the cortical stimulation affects to many behaviors and neurological process. This fact is observable both healthy subjects and patients with diverse neuropathologies, being the neuronal plasticity effect of tDCS its main encouraging aspect for future therapeutic programs. Specifically, the widely known positive effects of tDCS over motor functions, it does not matter cortical (M1), cerebellar or extra-encephalic disposition, and in pathological (Parkinson's disease, Restless syndrome, etc.) or healthy population (functioning of upper/lower limbs, etc.) administration, show that this device represents a fantastic opportunity to improve the rehabilitation effects of orthodoxical training-procedures. For this, the achievement of international protocols and safety guides which ensure a proper use of this technique are mandatory [89].

Basic research of neuroanatomical/functional structures are essential, with the main goal of generate the needed knowledge in order to work with reliably data for the development of more ideographic and specific programs of stimulation. On this sense, the improvement of neuroimaging techniques and scanners with a better neuroanatomical resolution is fundamental [89].

At a microscopic level, it is primary to still improving the researching on the biochemical base of tDCS in the human cortex, due to the current information do not let us to generate a complete theory about its action over the plastic mechanisms inherent to the human brain [90]. Added to this, the development of more sophisticated methodologies for the analysis of the axon orientation, the dendritic arborization, the role of astrocytes and the electrical field threshold of cortical cells is very important too [91].

Otherwise, its use in patients who are refractory to certain pharmacological treatments, as well as in those people in whose state (e.g. pregnancy) the pharmacological intervention is discouraged [92] is another guideline for non-invasive technologies in the future. Added to this last issue, tDCS could play a key role as a useful modulator of pharmacological treatments [93, 94].

The high impact in children with cerebral palsy of tDCS might be due to the general higher impact of its application in immature brains, as the electric peaks in children and adolescents are twice as higher than in adults by using the same parameters [74]. In addition, brain plasticity which characterizes these early ages could contribute to its potentiated effect. For this reason, in our point of view, the effect of tDCS on children is still needed to be further studied as well as the development stages of the CNS to ensure its safety.

The tDCS technique is already being used in the private as well as in the public clinic context. However, there are still some handicaps which should be taken into consideration on its application. Namely, the exact parameters which are effective for each particular pathology have to be defined. In addition, individual differences regarding the effect of tDCS are also a factor which is needed to be studied. Finally, mechanism of

action of tDCS must still be explained in order to exactly define the neurophysiology that underlies the present technique, which is a cue factor for its specific and safety use.

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References

1. Largus, S.: De Compositionibus Medicamentorum. Wechel, Paris (1529)
2. Kellaway, P.: The part played by the electric fish in the early history of bioelectricity and electrotherapy. Bull. Hist. Med. **20**, 112–137 (1946)
3. Zago, S., Ferrucci, R., Fregni, F., Priori, A.: Bartholow, Sciamanna, Alberti: pioneers in the electrical stimulation of the exposed human cerebral cortex. Neurosci. **14**(5), 521–528 (2008)
4. Priori, A., Hallett, M., Rothwell, J.C.: Repetitive transcranial magnetic stimulation or transcranial direct current stimulation? Brain Stimul. **2**(4), 241–245 (2009)
5. Pascual-Leone, A., Tormos-Muñoz, J.M.: Estimulación magnética transcraneal: fundamentos y potencial de la modulación de redes neurales específicas. Rev Neurol **46**(S1), S3–S10 (2008)
6. Kobayashi, M., Pascual-Leone, A.: Transcranial magnetic stimulation in neurology. Lancet Neurol. **2**(3), 145–156 (2003)
7. Nitsche, M.A., Cohen, L.G., Wassermann, E.M., Priori, A., Lang, N., Antal, A., et al.: Transcranial direct current stimulation: State of the art 2008. Brain Stimul. **1**(3), 206–223 (2008)
8. George, M.S., Aston-Jones, G.: Noninvasive techniques for probing neurocircuitry and treating illness: vagus nerve stimulation (VNS), transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS). Neuropsychopharmacol. **35**(1), 301–316 (2010)
9. Ruffini, G., Wendling, F., Merlet, I., Molaee-Ardekani, B., Mekonnen, A., Salvador, R., et al.: Transcranial current brain stimulation (tCS): models and technologies. IEEE Trans Neural Syst Rehab Eng. **21**(2), 333–345 (2013)
10. Costa, T., Lapenta, O., Boggio, P., Ventura, D.: Transcranial direct current stimulation as a tool in the study of sensory-perceptual processing. Atten., Percept., Psychophys. **77**(6), 1813–1840 (2015)
11. Nitsche, M.A., Doemkes, S., Karaköse, T., Antal, A., Liebetanz, D., Lang, N., et al.: Shaping the effects of transcranial direct current stimulation of the human motor cortex. J. Neurophysiol. **97**(4), 3109–3117 (2007)
12. Bastani, A., Jaberzadeh, S.: a-tDCS differential modulation of corticospinal excitability: The effects of electrode size. Brain Stimul. **6**(6), 932–937 (2013)
13. Faria, P., Hallett, M., Miranda, P.C.: A finite element analysis of the effect of electrode area and inter-electrode distance on the spatial distribution of the current density in tDCS. J. Neural Eng. **8**(6), 1–24 (2011)
14. Minhas, P., Datta, A., Bikson, M.: Cutaneous perception during tDCS: Role of electrode shape and sponge salinity. Clin. Neurophysiol. **122**(4), 637–638 (2011)
15. Bikson, M., Datta, A., Elwassif, M.: Establishing safety limits for transcranial direct current stimulation. Clin. Neurophysiol. **120**(6), 1033–1034 (2009)
16. Nitsche, M.A., Fricke, K., Henschke, U., Schlitterlau, A., Liebetanz, D., Lang, N., et al.: Pharmacological modulation of cortical excitability shifts induced by transcranial direct current stimulation in humans. J. Physiol. **553**(pt1), 293–301 (2003)

17. Nitsche, M.A., Niehaus, L., Hoffmann, K.T., Hengst, S., Liebetanz, D., Paulus, W., et al.: MRI study of human brain exposed to weak direct current stimulation of the frontal cortex. Clin. Neurophysiol. **115**(10), 2419–2423 (2004)
18. Kwon, Y.H., Ko, M.H., Ahn, S.H., Kim, Y.H., Song, J.C., Lee, C.H., et al.: Primary motor cortex activation by transcranial direct current stimulation in the human brain. Neurosci Lett. **435**(1), 56–59 (2008)
19. Lang, N., Siebner, H.R., Ward, N.S., Lee, L., Nitsche, M.A., Paulus, W., et al.: How does transcranial DC stimulation of the primary motor cortex alter regional neuronal activity in the human brain? Euro J. Neurosci. **22**(2), 495–504 (2005)
20. Ardolino, G., Bossi, B., Barbieri, S., Priori, A.: Non-synaptic mechanism sunderlie the after-effects of cathodal transcutaneous direct current stimulation of the human brain. J. Physiol. **568**, 653–663 (2005)
21. Lefaucheur, J.P.: Principles of therapeutic use of transcranial and epidural cortical stimulation. Clin. Neurophysi. **119**(10), 2179–2184 (2008)
22. Boggio, P.S., Zaghi, S., Fregni, F.: Modulation of emotions associated with images of human pain using anodal transcranial direct current stimulation (tDCS). Neuropsychol. **47**(1), 212–217 (2009)
23. Boggio, P.S., Zaghi, S., Lopes, M., Fregni, F.: Modulatory effects of anodal transcranial direct current stimulation on perception and pain thresholds in healthy volunteers. Eur. J. Neurol. **15**(10), 1124–1130 (2008)
24. Miranda, P.C., Lomarev, M., Hallett, M.: Modeling the current distribution during transcranial direct current stimulation. Clin. Neurophysiol. **117**(7), 1623–1629 (2006)
25. Nitsche, M.A., Paulus, W.: Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans. Neurol. **57**(10), 1899–1901 (2001)
26. Been, G., Ngo, T.T., Miller, S.M., Fitzgerald, P.B.: The use of tDCS and CVS as methods of non-invasive brain stimulation. Brain Res. Rev. **56**(2), 346–361 (2007)
27. Parasuraman, R., McKinley, R.A.: Using noninvasive brain stimulation to accelerate learning and enhance human performance. Hum. Factors J. Hum. Factor Ergon. Soc. **56**(5), 816–824 (2014)
28. Rango, M., Cogiamanian, F., Marceglia, S., Barberis, B., Arighi, A., Biondetti, P., et al.: Myoinositol content in the human brain is modified by transcranial direct current stimulation in a matter of minutes: a 1H-MRS study. Magn. Reson. Med. **60**(4), 782–789 (2008)
29. Merzagora, A.C., Foffani, G., Panyavin, I., Mordillo-Mateos, L., Aguilar, J., Onaral, B., et al.: Prefrontal hemodynamic changes produced by anodal direct current stimulation. Neuroimage. **49**(3), 2304–2310 (2010)
30. Molaee-Ardekani, B., Márquez-Ruiz, J., Leal-Campanario, R., Gruart, A., Merlet, I., Birot, G., et al.: Effects of transcranial direct current stimulation (tDCS) on sensory evoked potentials: a computational modeling study. Brain Stimul. **6**(1), 25–39 (2013)
31. Chaieb, L., Antal, A., Paulus, W.: Gender-specific modulation of short-term neuroplasticity in the visual cortex induced by transcranial direct current stimulation. Visual Neurosci. **25**(1), 77–81 (2008)
32. Fritsch, B., Reis, J., Martinowich, K., Schambra, H.M., Ji, Y., Cohen, L.G., et al.: Direct current stimulation promotes BDNF-dependent synaptic plasticity: potential implications for motor learning. Neuron **66**(2), 198–204 (2010)
33. Liebetanz, D., Nitsche, M.A., Tergau, F., Paulus, W.: Pharmacological approach to the mechanisms of transcranial DC-stimulation-induced after-effects of human motor cortex excitability. Brain. **125**(pt10), 2238–2247 (2002)

34. Charlotte, J.S., Jonathan, G.B., Stephenson, M.C., O'Shea, J., Wylezinska, M., Kincses, Z.T., et al.: Polarity-sensitive modulation of cortical neurotransmitters by transcranial stimulation. J. Neurosc. **29**(16), 5202–5206 (2009). doi:10.1523/JNEUROSCI.4432-08.2009
35. Nitsche, M.A., Grundey, J., Liebetanz, D., Lang, N., Tergau, F., Paulus, W.: Catecholaminergic consolidation of motor cortical neuroplasticity in humans. Cereb. Cortex **14**(11), 1240–1245 (2004)
36. Nitsche, M.A., Kuo, M.F., Karrasch, R., Wachter, B., Liebetanz, D., Paulus, W.: Serotonin affects transcranial direct current-induced neuroplasticity in humans. Biol. Psychiatry **66**(5), 503–508 (2009)
37. Izumi, Y., Zorumski, C.F.: Direct cortical inputs erase long-term potentiation at Schaffer collateral synapses. J. Neurosci. **28**(38), 9557–9563 (2008)
38. Márquez-Ruiz, J., Leal-Campanario, R., Sánchez-Campusano, R., Molaee-Ardekani, B., Wendling, F., Miranda, P., et al.: Transcranial direct-current stimulation modulates synaptic mechanisms involved in associative learning in behaving rabbits. PNAS **109**(17), 6710–6715 (2012)
39. Kuo, M.F., Paulus, W., Nitsche, M.A.: Boosting focally-induced brain plasticity by dopamine. Cereb. Cortex **18**(3), 648–651 (2008)
40. Poreisz, C., Boros, K., Antal, A., Paulus, W.: Safety aspects of transcranial direct current stimulation concerning healthy subjects and patients. Brain Res. Bull. **72**(4–6), 208–214 (2007)
41. Nitsche, M.A., Paulus, W.: Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. J. Physiol. **527**, 633–639 (2000)
42. Iyer, M.B., Mattu, U., Grafman, J., Lomarev, M., Sato, S., Wassermann, E.M.: Safety and cognitive effect of frontal DC brain polarization in healthy individuals. Neurology. **64**(5), 872–875 (2005)
43. Wassermann, E.M., Grafman, J.: Recharging cognition with DC brain polarization. Trends Cogn. Sci. **9**(11), 503–505 (2005)
44. Vandermeeren, Y., Jamart, J., Ossemann, M.: Effect of tDCS with an extracephalic reference electrode on cardio-respiratory and autonomic functions. BMC Neurosci. **11**, 38 (2010)
45. Palm, U., Keeser, D., Schiller, C., Fintescu, Z., Reisinger, E., Padberg, F., et al.: Skin lesions after treatment with trancranial direct current stimulation (tDCS). Brain Stimul. **1**(4), 386–387 (2008)
46. Tanaka, S., Watanabe, K.: Transcranial direct current stimulation: a new tool for human cognitive neuroscience. Brain Nerve **61**, 53–64 (2009)
47. Lindenberg, R., Renga, V., Zhu, L.L., Nair, D., Schlaug, G.: Bihemispheric brain stimulation facilitates motor recovery in chronic stroke patients. Neurology. **75**(24), 2176–2184 (2010)
48. Schlaug, G., Renga, V., Nair, D.: Transcranial direct current stimulation in stroke recovery. Arch. Neurol. **65**(12), 1571–1576 (2008)
49. O'Shea, J., Boudrias, M.H., Stagg, C.J., Bachtiar, V., Kischka, U., Blicher, J.U., et al.: Predicting behavioral response to TDCS in chronic motor stroke. NeuroImage. **85**, 924–933 (2014)
50. Hummel, F., Celnik, P., Giraux, P., Floel, A., Wu, W.H., Gerloff, C., et al.: Effects of non-invasive cortical stimulation on skilled motor function in chronic stroke. Brain. **128**(3), 490–499 (2005)
51. Sattler, V., Acket, B., Gerdelat-Mas, A., Raposo, N., Albucher, J.F., Thalamas, C., et al.: Effect of repeated sessions of combined anodal tDCS and peripheral nerve stimulation on motor performance in acute stroke: A behavioral and electrophysiological study. Ann Phys Rehab Med. **55**(S1), S5–S6 (2012)

52. Rosso, C., Perlbarg, V., Valabregue, R., Arbizu, C., Ferrieux, S., Alshawan, B., et al.: Broca's area damage is necessary but not sufficient to induce after-effects of cathodal tDCS on the unaffected hemisphere in post-stroke aphasia. Brain Stimul. **7**(5), 627–635 (2014)
53. Málly, J.: Non-invasive brain stimulation (rTMS and tDCS) in patients with aphasia: Mode of action at the cellular level. Brain Res. Bull. **98**, 30–35 (2013)
54. Gordon, C., Hewer, R.L., Wade, D.T.: Dysphagia in Acute Stroke. Br. Med. J. (Clin. Res. Ed). **295**, 411–414 (1987)
55. Barer, D.H.: The Natural History and Functional Consequences of Dysphagia after Hemispheric Stroke. J. Neurol. Neurosurg. Psychiatry **52**(2), 236–241 (1989)
56. Martin, R.E., Sessle, B.J.: The Role of the Cerebral Cortex in Swallowing. Dysphagia **8**(3), 195–202 (1993)
57. Hamdy, S., Rothwell, J.C., Aziz, Q., Thompson, D.G.: Organization and reorganization of human swallowing motor cortex: implications for recovery after stroke. Clin. Sci. **99**(2), 151–157 (2000)
58. Sandrini, M., Cohen, L.G.: Noninvasive brain stimulation in neurorehabilitation. Handb Clin. Neurol. **116**, 499–524 (2013)
59. Kumar, S., Wagner, C.W., Frayne, C., Zhu, L., Selim, M., Feng, W., et al.: Noninvasive brain stimulation may improve stroke-related dysphagia: a pilot study. Stroke **42**(4), 1035–1040 (2011)
60. Yang, E.J., Baek, S.R., Shin, J., Lim, J.Y., Jang, H.J., Kim, Y.K., et al.: Effects of transcranial direct current stimulation (tDCS) on post-stroke dysphagia. Restor Neurol Neurosci. **30**(4), 303–311 (2012)
61. Broeder, S., Nackaerts, E., Heremans, E., Vervoort, G., Meesen, R., Verheyden, G., et al.: Transcranial direct current stimulation in Parkinson's disease: Neurophysiological mechanisms and behavioral effects. Neurosci. Biobehav. Rev. **57**, 105–117 (2015)
62. Fregni, F., Boggio, P.S., Santos, M.C., Lima, M., Vieira, A.L., Rigonatti, S.P., et al.: Noninvasive cortical stimulation with transcranial direct current stimulation in Parkinson's disease. Mov. Disord. **21**, 1693–1702 (2006)
63. Valentino, F., Cosentino, G., Brighina, F., Pozzi, N.G., Sandrini, G., Fierro, B., et al.: Transcranial direct currentstimulation for treatment of freezing of gait: a cross-over study. Mov. Disord. **29**, 1064–1069 (2014)
64. Benninger, D.H., Lomarev, M., Lopez, G., Wassermann, E.M., Li, X., Considine, E., et al.: Transcranial direct current stimulation for the treatment of Parkinson's disease. J. Neurol. Neurosurg. Psychiatry **81**, 1105–1111 (2010)
65. Kaski, D., Allum, J.H., Bronstein, A.M., Dominguez, R.O.: Applying anodal tDCS during tango dancing in a patient with Parkinson's disease. Neurosci. Lett. **568**, 39–43 (2014)
66. Pereira, J.B., Junqué, C., Bartrés-Faz, D., Martí, M.J., Sala-Llonch, R., Compta, Y.: Modulation of verbal fluency networks by transcranial direct current stimulation (tDCS) in Parkinson's disease. Brain Stimul. **6**, 16–24 (2013)
67. Mehta, S., McIntyre, A., Guy, S., Teasell, R.W., Loh, E.: Effectiveness of transcranial direct current stimulation for the management of neuropathic pain after spinal cord injury: a meta-analysis. Spinal Cord. **53**(11), 780–785 (2015)
68. Silva, F.T.G., Rêgo, J.T.P., Raulino, F.R., Silva, M.R., Reynaud, F., Egito, E.S.T., et al.: Transcranial direct current stimulation on the autonomic modulation and exercise time in individuals with spinal cord injury: A case report. Autonomic Neurosci : Basic Clin. **193**, 152–155 (2015)

69. Murray, L.M., Edwards, D.J., Ruffini, G., Labar, D., Stampas, A., Pascual-Leone, A., et al.: Intensity dependent effects of transcranial direct current stimulation on corticospinal excitability in chronic spinal cord injury. Arch. Phys. Med. Rehab. **96**(4 Suppl), S114–S121 (2015)
70. Hubli, M., Dietz, V., Schrafl-Altermatt, M., Bolliger, M.: Modulation of spinal neuronal excitability by spinal direct currents and locomotion after spinal cord injury. Clin Neurophysiol: Off. J. Inter. Fed. Clin. Neurophysiol. **124**(6), 1187–1195 (2013)
71. Cogiamanian, F., Vergari, M., Pulecchi, F., Marceglia, S., Priori, A.: Effect of spinal transcutaneous direct current stimulation on somatosensory evoked potentials in humans. Clin Neurophysiol: Off. J. Inter. Fed. Clin. Neurophysiol. **119**(11), 2636–2640 (2008)
72. de Almeida, J.R., Guyatt, G.H., Sud, S., Dorion, J., Hill, M.D., Kolber, M.R., et al.: Management of bell palsy: clinical practice guideline. CMAJ **186**, 917–922 (2014)
73. Swaiman, K.F.: Cerebral palsy. In: Swaiman, K.F., Ashwal, S., Ferriero, D.M., Schor, N.F. (eds.) Swaiman's Pediatric Neurology: Principles and Practice, 5th edn, pp. 999–1008. St. Louis: Elsevier, New York (2012)
74. Minhas, P., Bikson, M., Woods, A.J., Rosen, A.R., Kessler, S.K.: Transcranial direct current stimulation in pediatric brain: a computational modeling study. In: Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC) (2012)
75. Bax, M., Tydeman, C., Flodmark, O.: Clinical and MRI correlates of cerebral palsy: the european cerebral palsy study. JAMA **296**, 1602–1608 (2006)
76. Lance, J.W.: Pathophysiology of Spasticity and Clinical Experience with Baclofen. In: Feldman, R.G., Young R.R., Koella, W.P., (eds.) Spasticity, Disordered Motor Control. Miami, FL: Symposia Specialists, pp. 185–203 (1980)
77. Aree-uea, B., Auvichayapat, N., Janyacharoen, T., Siritaratiwat, W., Amatachaya, A., Prasertnoo, J., et al.: Reduction of spasticity in cerebral palsy by anodal transcranial direct current stimulation. J. Med. Assoc. Thai. **97**(9), 954–962 (2014)
78. Lazzari, R.D., Politti, F., Santos, C.A., Dumont, A.J.L., Rezende, F.L., Grecco, L.A.C., et al.: Effect of a single session of transcranial direct-current stimulation combined with virtual reality training on the balance of children with cerebral palsy: a randomized, controlled, double-blind trial. J. Phys Ther. Sci. **27**(3), 763–768 (2015)
79. Grecco, L.A.C., de Almeida, N., Mendonça, M.E., Galli, M., Fregni, F., Santos, C.: Effects of anodal transcranial direct current stimulation combined with virtual reality for improving gait in children with spastic diparetic cerebral palsy: a pilot, randomized, controlled, double-blind, clinical trial. Clin Rehabil. **29**(12), 1212–1223 (2015)
80. Palm, U., Ayache, S.S., Padberg, F., Lefaucheur, J.-P.: Non-invasive brain stimulation therapy in multiple sclerosis: a review of tDCS, rTMS and ECT results. Brain Stimul. **7**(6), 849–854 (2014)
81. Cuypers, K., Leenus, D.J.F., Van Wijmeersch, B., Thijs, H., Levin, O., Swinnen, S.P., et al.: Anodal tDCS increases corticospinal output and projection strength in multiple sclerosis. Neurosci. Lett. **554**, 151–155 (2013)
82. Meesen, R.L.J., Thijs, H., Daphnie, J.F., Leenus, D.J.F., Cuyper, K.: A single session of 1 mA anodal tDCS-supported motor training does not improve motor performance in patients with multiple sclerosis. Restore Neurol Neurosci. **32**(2), 293–300 (2014)
83. Mori, F., Nicoletti, C.G., Kusayanagi, H., Foti, C., Restivo, D.A., Marciani, M.G., et al.: transcranial direct current stimulation ameliorates tactile sensory deficit in multiple sclerosis. Brain Stimul. **6**(4), 654–659 (2013)
84. Mori, F., Codeca, C., Kusayanagi, H., Monteleone, F., Buttari, F., Fiore, S., et al.: Effects of anodal transcranial direct current stimulation on chronic neuropathic pain in patients with multiple sclerosis. J. Pain. **11**(5), 436–442 (2010)

85. Di Lazzaro, V., Ranieri, F., Capone, F., Musumeci, G., Dileone, M.: Direct current motor cortex stimulation for amyotrophic lateral sclerosis: a proof of principle study. Brain Stimul: Basic, Transl., Clin. Res. Neuromodul. **6**(6), 969–970 (2015)
86. Munneke, M.A., Stegeman, D.F., Hengeveld, Y.A., Rongen, J.J., Schelhaas, H.J., Zwarts, M.J.: Transcranial direct current stimulation does not modulate motor cortex excitability in patients with amyotrophic lateral sclerosis. Muscle Nerve **44**(1), 109–114 (2011)
87. Quartarone, A., Lang, N., Rizzo, V., Bagnato, S., Morgante, F., Sant'angelo, A., et al.: Motor cortex abnormalities in amyotrophic lateral sclerosis with transcranial direct-current stimulation. Muscle Nerve. **35**(5), 620–624 (2007)
88. Munneke, M.A.M., Rongen, J.J., Overeem, S., Schelhaas, H.J., Zwarts, M.J., Stegeman, D.F.: Cumulative effect of 5 daily sessions of θ burst stimulation on corticospinal excitability in amyotrophic lateral sclerosis. Muscle Nerve **48**(5), 733–738 (2013)
89. Brunoni, A.R., Nitsche, M.A., Bolognini, N., Bikson, M., Wagner, T., Merabet, L., et al.: Clinical research with transcranial direct current stimulation (tDCS): Challenges and future directions. Brain Stimul. **5**(3), 175–195 (2012)
90. Javadi, A.H., Cheng, P.: Transcranial direct current stimulation (tDCS) enhances reconsolidation of long-term memory. Brain Stimul. **6**(4), 668–674 (2012)
91. Radman, T., Ramos, R.L., Brumberg, J., Bikson, M.: Role of cortical cell type and morphology in subthreshold and suprathreshold uniform electric field stimulation. Brain Stimul. **2**(4), 215–228 (2009)
92. Zhang, X., Liu, K., Sun, J., Zheng, Z.: Safety and feasibility of repetitive transcranial magnetic stimulation (rTMS) as a treatment for major depression during pregnancy. Arch Womens Ment Health. **13**(4), 369–370 (2010)
93. Brunoni, A.R., Ferrucci, R., Bortolomasi, M., Scelzo, E., Boggio, P.S., Fregni, F., et al.: Interactions between transcranial direct current stimulation (tDCS) and pharmacological interventions in the Major Depressive Episode: Findings from a naturalistic study. Eur Psychiatry. **28**(6), 356–361 (2013)
94. Brunoni, A.R., Valiengo, L., Baccaro, A., Zanão, T.A., de Oliveira, J.F., Goulart, A., et al.: The Sertraline vs. electrical current therapy for treating depression clinical study: Results from a factorial, randomized, controlled trial. JAMA Psychiatry. **32**(1), 90–98 (2013)