

Efficacy of Transcranial Direct Current Stimulation as Support for Neurorehabilitation Therapy: A Meta-analysis of Available Studies

Banchetti PA* and Marini C

Department of Life, Health and Environmental Sciences, University of L'Aquila, Italy

*Corresponding author: Paola Andrea Banchetti, Research Fellow, Department of Life, Health and Environmental Sciences, University of L'Aquila, Italy, Tel: 3922629062; E-mail: andrea.banchetti03@gmail.com

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Abstract

Transcranial direct current stimulation (tDCS) is a non-invasive, well-tolerated, brain stimulation technique, using a weak current applied on the scalp. Rationale of tDCS use has been based on the assumption of the post-stroke inter-hemispheric competition model, resulting in a hypo-excitability hemispheric lesion and a hyper-excitability healthy hemisphere, to improve the recovery of motor function. Several small studies have been published but the efficacy of tDCS is not established. We performed a systematic review of published studies to assess efficacy of tDCS on motor function of patients with stroke. A thorough search of main databases has been performed to identify randomized, controlled studies on efficacy of tDCS in patients with stroke. The values derived from the primary outcome measures of these studies have been standardized to make them comparable; eight comparisons were planned: degree of dependence, improvement of upper limb, improvement of global motor function, improvement of lower limb and visual perception; comparison between anode stimulation and sham, anode stimulation and follow-up. 8 studies have been included in the meta-analysis. 3 studies have been excluded because of lack of statistical data, non-randomized assignment and lack of a control group; 178 participants have been included altogether. Most of comparisons did not produce significant results; however a significant improvement of dependence scores ($p=0.02$), of lower limb index ($p=0.02$), and of visual perception ($p=0.02$) have been found. Despite the encouraging results by neurophysiological and instrumental investigations, in some heterogeneous cases, our study shows that there is a need to conduct studies with larger sample sizes.

Keywords: Neurorehabilitation therapy; Motor function; Limb; Neurophysiological; Stroke

Introduction

Transcranial direct current stimulation (tDCS) is a noninvasive, well-tolerated, bidirectional brain stimulation technique whose use does not result in the occurrence of auditory and somatosensory perceptions after the initial minutes [1-5], using a weak current applied on the scalp, through two electrodes of sponge soaked in saline solution to modulate spontaneous neuronal discharge frequency in painless and reversible [6,7]. The effects are polar-dependent; Anodal stimulation induces depolarization of the neural membrane, while cathodal stimulation induces hyperpolarization [8,9].

In many recent studies, ratio of tDCS has been based by assumption of the post-stroke inter-hemispheric competition model, resulting in a hypo-excitability hemispheric lesion and a hyper-excitability healthy hemisphere, to improve the recovery of motor function. Some studies suggest that the amount of transcallosal inhibition may be positively linked to the degree of motor disability [10,6], making it plausible the hypothesis that this phenomenon is a maladaptive process with effects resulting from the impairment of motor function [11].

Material and Methods

Literature research and selection of studies

Eight studies were considered for a total of 178 subjects included [6,12-18]. Computer literacy research has been focused on post-stroke

motor recovery studies by administering non-invasive brain stimulation (NIBS) including transcranial direct current stimulation (tDCS); the research period of the literature is between January 2005 and May 2016. The databases used were two: PubMed and Cochrane Database of Systematic Reviews. Five key words were used: (a) stroke (b) brain infarct (c) rehabilitation (d) tDCS (e) NIBS.

All studies were evaluated for inclusion and exclusion criteria to minimize the risk of bias. Inclusion criteria were: quantification of tDCS effects on motor recovery, comparison between group (i.e. anode, cathode and bilateral stimulation). Studies that did not report both the randomized assignment and the control group were excluded. The exclusion criteria were: review articles, case studies, case reports, studies that did not report statistical data, and studies without control group. 6/8 studies are RCT, the other two are cross-over tracks. 6/8 have tDCS rehabilitation protocols, 5 of them simultaneously with tDCS, while 1/8 administer rehabilitation intervention after brain stimulation. Eight comparisons were considered: variations in patient dependence, upper limb recovery, lower limb motor recuperation, global motor function, visual perception, anodal vs. cathodal stimulation (inherent to global motor recovery), anodal stimulation vs. sham and anodal stimulation vs. sham follow-up (inherent to upper motor recovery).

Valuation scales

Primary assessment measures were Fugl-Meyer Upper Limb (FM-UL), Jebsen Taylor Hand Function Test (JTHFT), Finger Flexion Scale (Bhakta fist) for upper limbs; Wolf Motor Function Test (WMFT) Fugl-Meyer Assessment and European Stroke Scale for Improving

Motor Functionality; Lower Limb Motricity Index as a lower limb evaluation; Motor free Visual Perception Test for visual perception; Barthel Index and Functional Independence Measure as Dependency/ Independence Assessment Scales.

Publication	Extremity	Recovery phase	Number of sessione (x) and days per week (DPW)	Anodal (a), cathodal (c) bilateral (b) sham (s)	tDCS duration min	tDCS intensity (mA)	Training (Tx)	Sequence of tDCS and Tx	Effect	Study design
Lindenberg et al. 2010 (n=20)	Upper	Chronic	5x consecutive days	B,S	30 min	1,5 mA	60 min PT/TO	During Tx	↑	RCT
Ko-Un Kim et al. 2016 (n=30)	Visual perception	Chronic	30x5 WPD weekays only	B,S	20 min	1 mA	30 min TO	During Tx	↑	RCT
F. Hummel et al. 2005 (n=6)	Upper	Chronic	1x	B,S	20 min	1 mA	n/a	n/a	↑	NRCOT
S. Straudi et al. 2016 (n=23)	Upper	Chronic/subacute	10x5 WPD weekdays only	B,S	30 min	1 mA	30 min Robot-assisted therapy upper limb	During Tx	NSD	RCT
M.C. Chang et al. 2015 (n=24)	Lower	Subacute	10x5 WPD weekdays only	A,S	10 min	2 mA	PT	During Tx	↑ lower limb	RCT
S. Rocha et al. 2015 (n=21)	Upper	Chronic	12x3 WPD	A,C,S	13 min A, 9 min C	1 mA	6h mCIMT	Before Tx	↑ A,C	NRCOT
A. Del Felice et al. 2016 (n=10)	Upper	Chronic	5x consecutive days	A,C,S	20 min	1 mA	n/a	n/a	↑ A,C	NRCOT
K. Figlewski et al. 2016 (n=44)	Upper	Chronic	9x consecutive days	B,S	30 min	1,5 mA	CIMT	During Tx	↑ motor	RCT

↑ Positive effect; NSD no significant difference; OT/PT occupational therapy/physical therapy; mCIMT, Constraint-induced movement therapy; CIMT, Constraint-induced movement therapy; RCT, randomized Controlled Trial; NRCOT, Non-Randomized Crossover Trial

Figure 1: Presents the main features of the studies.

The values derived from the above scales have been standardized to make them comparable, indicative of a common parameter, in a generalized improvement scale of the coded performance as the number of standard deviations from the average performance of the group. Review Manager 5.3 (RevMan) version 5.3.5, Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration 2014 has been used.

Results

From the analysis of literature, 11 studies have been identified with the characteristics specified in the inclusion criteria; 3 studies were not included in the analysis due to the exclusion criteria. The summary table (Figure 1) presents the main features of the studies included.

The total study participants were 178, 118 males, 60 females. The age range ranged from 34 to 84. Most subjects have chronic stroke, only

one study includes only subacute subjects (7-30 days from the event) [16], and another study included both [15]. Bilateral stimulation was administered in majority of trails, while in 2 studies anodal stimulation was investigated [16] and cathodal stimulation in one study [18]; The current intensity varies from 1 mA to 2 mA. In most studies the hemisphere affected by the anode electrode and the cathode electrode positioned on the hemisphere has been stimulated; only 3 studies have used monocephalic montage [6,16,18]. The duration of stimulation ranged from 9 min to 30 min. The treatment protocol, in addition to neuromodulation, in most cases provided for a physiotherapy and/or occupational or robotic rehabilitation program, concurrently with stimulation, only one study included post-tDCS rehabilitation therapy [6], whereas in 2 studies it was present only neuromodulation [14,18].

In most cases the evaluation is inherent to the upper limb, in a trial the first measure was the response to the treatment of the lower limb [16] and in one studies the effects on visual perception [13].

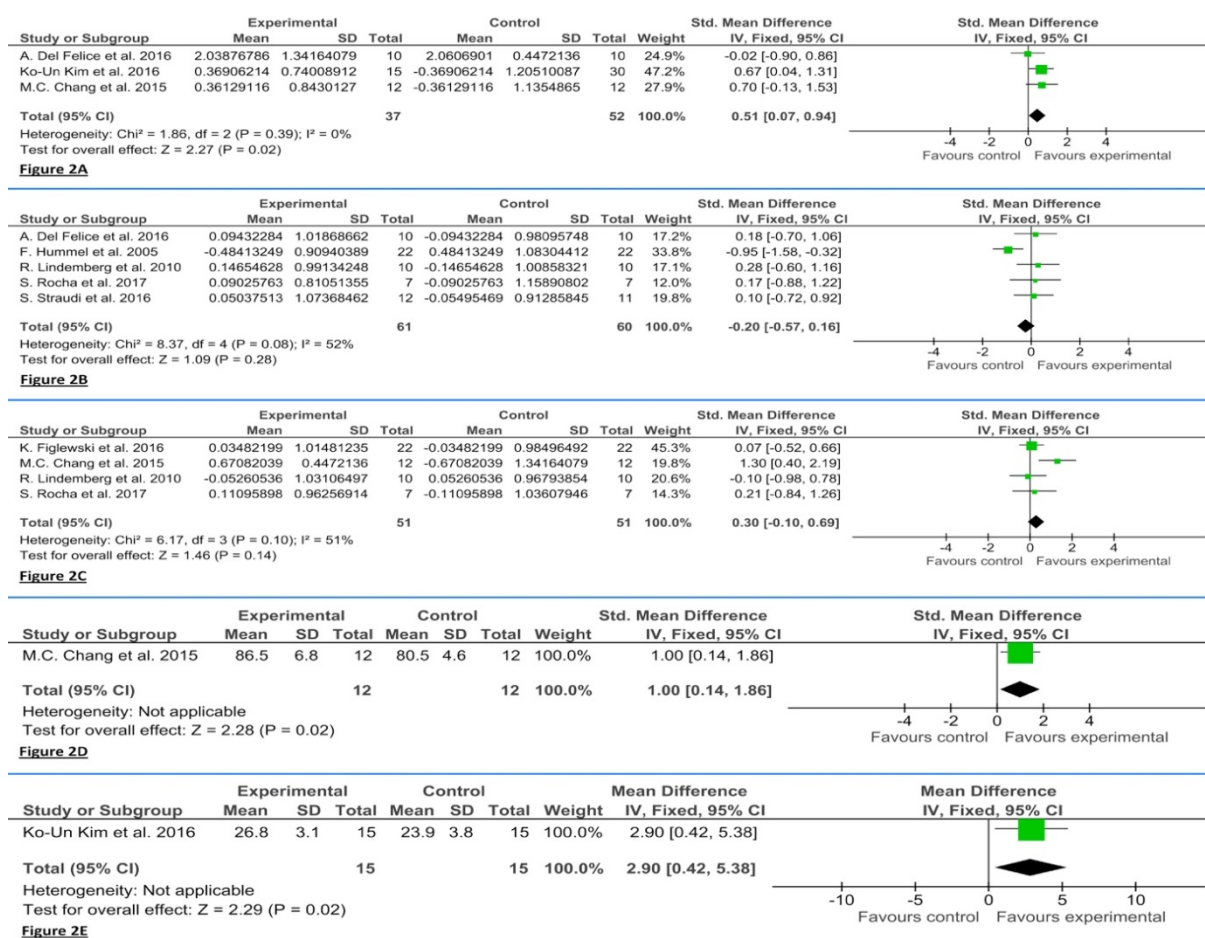


Figure 2: Presents subgroup study findings.

In the assessment of dependency, the analysis for comparison of active vs. sham treatment showed, as in Figure 2A, a statistically significant reduction ($p=0.02$) of the dependency rate after tDCS treatment, with a standardized score difference of 0.51 (95% CI 0.07-0.94), without significant heterogeneity among studies ($p=0.39$).

There was no significant difference between studies ($p=0.28$) due to heterogeneity between studies ($p=0.08$) as compared to the upper limb function as recited in Figure 2B.

The analysis of the effect on the overall motor function of pacing with the active electrode vs. control group showed a trend in favour of experimental treatment which does not yet achieve statistical significance ($p=0.14$) (Figure 2C).

Comparison with active stimulation vs. sham stimulation was effective in improving the lower limb scale, as in Figure 2D (SMD=1.00; 95% CI 0.14-1.86), and in improving the visual perception functionality (SMD=2.90; 95% CI 0.42-5.38) (Figure 2E).

The administration of anodal stimulation vs. sham was significantly effective ($p=0.02$) in improving the upper limb function (SMD=0.81, 95% CI 0.13-1.49).

Only one study analysed the long-term differences in the function of the upper limb without any significant differences $p=0.68$.

No difference was found between dual stimulation and cathodal stimulation with respect to motor function improvement ($p=0.50$).

Discussion

Six studies involving eight used a bilateral montage, including the anodal stimulation of M1 of the ipsilesional hemisphere (C3 and C4 EEG 10/20 system), cathodal stimulation of M1 of the contralesional hemisphere or cathodal stimulation of the contralateral supraorbital area to the lesion [12-19]. Bilateral montage is often used based on the assumption that the movements of the impaired limbs are often associated with a high level of transcallosal inhibition by the hemisphere not affected by the hemisphere being injured [10,20]; some studies conducted with multimodal imaging techniques and mapping, such as fMRIs and TMSs, confirmed the existence of this imbalance of the hemisphere not affected, also called a hemispheric competition model, particularly during the preparation and execution of upper-limb motor acts [21,22], some authors hypothesize that the amount of this imbalance in inter-hemispheric excitability may be positively correlated with the degree of severity of motor disability [10,6]. Lindenberg et al. found significant and extensive improvement in

motor function in the stimulated group, stimulation with simultaneous rehabilitation treatment based on physiotherapy techniques and occupational therapy with compared to the control group; the effects are verifiable even after one week after the end of the treatment; it has also been hypothesized that the magnitude of the electrode may affect the adjacent premotor cortex as well as the anodic somatosensory cortex; similarly, cathodal stimulation may have a similar effect in adjacent structures [19]. In the same study, the activation of post-stimulation cerebral areas by fMRI was investigated, denoting a greater activation of the ipsilesional motor area in the active group, in contrast to the control group; activation changes were detected dorsally to the motor area, giving a typical limbic representation.

Kim et al. using a bi-hemispheric montage simultaneous to occupational therapy, found an approximate improvement of six points in the experimental group compared to the control group in the evaluation of the function of visual perception; while an increase of 13 points is denoted in the assessment of dependence/independence in the experimental group. Hummel et al. denotes a significant difference between tDCS-induced improvements for tasks requiring fine and distal motor control versus tasks involving proximal compartments. The study conducted by Chang et al. with bilateral montage and simultaneous rehabilitation treatment including physiotherapy protocols, showed a significantly higher improvement in the experimental group in relation to the motor recovery of the lower limb compared to the sample group.

Five out of eight studies contributed to the administration of tDCS to the rehabilitation treatment, reporting a significant increase compared to the control groups [12,13,16,17]; Straudi et al. using Upper Extremity Robot-Assisted Training however showed a general improvement in motor function in both groups, and the lack of significant superiority between the experimental group and the control group. It has been hypothesized that peripheral training, meant as functional motor tasks designed to promote sensorimotor integration, coordination of movements and goal-directed activities of practical relevance [12], in combination with tDCS could improve the acquisition of motor skills and the respective consolidation of the same through a mechanism LTD due to the increase in inputs versus the cortex while its intrinsic excitability is modified by tDCS [23]. In a particular way the Long Term Potentiation mechanism determines a long-term increase of synapse efficiency, and long-term depression (LTD) translated in a diminution in synapse efficiency, are mechanisms that occur in the cerebral cortex and are strongly implicated as a primary factor in motor learning and brain plasticity, this could clarify the effects of tDCS [24]. The explanation derives from the assertion for which NMDA receptor modulation plays an important role for the propagation of LTP and LTD, bringing a facilitation when the post-synaptic membranes, soma and dendritic are depolarized [25], when the area underlying the stimulation is closer to the negative pole of the electric field, facilitates the opening of voltage-dependent ionic channels with consequent activation of the NMDA receptors by removing the magnesium ions block Mg^{2+} [26]. Anodal stimulation could therefore activate the NMDA receptors, potentially translating into a significant increase of Ca^{2+} in post-synaptic cells [23]; it is therefore hypothesized that facilitation in motor learning through repeated tDCS sessions can be explained as the result of an additional effect on the post-synaptic levels of Ca^{2+} , which leads to a long-term change in synaptic efficiency [23]. The effects on ion channels of Ca^{2+} and on NMDA receptors may be dependent on the concurrently reduction of the GABA-ergic tone, always facilitated by anode stimulation [18,27,28].

As a physical therapy associated with tDCS some authors use the modified Constraint-Induced Moving Therapy (mCIMT); in the study considered emerged a significant interaction time effect and time x group in the upper limb and motor function evaluations for the experimental group, in both times of verification (T1 and follow-up), demonstrating a mild maintenance of the effects between post-intervention and follow-up in the group to which anodal stimulation was administered, compared to cathodal stimulation and sham [6].

Some authors have demonstrated the effectiveness of CIMT in improving the motor function of the upper limb post-stroke; in accordance with the model of inter-hemispheric imbalance, increasing the hemispheric activity by limiting the contralateral hemisphere activity [29,30]; a healthy limb retention for 90% of waking time, and a specific training of the affected limb for 6 h each day [31], while mCIMT reduces the retention time of the healthy limb for six continuous hours and the administration of specific tasks to be performed by the affected limb of one-hour duration [29,32-34]. The covariant analysis also presents the stage of the lesion, some studies include only chronic stroke, other subacute stroke, or both. In this meta-analysis studies including subjects with chronic stroke are 6, 1 with subacute stroke and 1 with both. Some evidence [15,35-37] points out, an improvement in the results of subjects with chronic stroke, associated with rehabilitative treatment; Straudi hypothesizes that, according to the model of inter-hemispheric competition, in the subacute phase the increase of the cortical excitability of the contralateral hemisphere to the lesion can be compensatory rather than maladaptive; in this stage, the effects of neuromodulation may be masked by spontaneous recovery, with little further clarity; motor training, in addition, induces a cortical reorganization after a few weeks from the end of treatment suggesting that early rehabilitation therapy could involve the evolution of neural post-stroke networks [12,38].

Instrumental studies, showed through transcranial magnetic stimulation (TMS) cortical excitability, an increase of recruitment curves correlated with improved tDCS induced motor performance, and a shortened intra-cortical inhibition interval [14]; neurophysiological evaluation of the cathodal vs. dual stimulation revealed a slight increase in the H wave reflex latency in both stimulations, cathodal stimulation maintained modulation of H reflection for a slightly longer period [18]. The H-reflex is a spinal monosynaptic reflex that measures the excitability of alpha motoneuron, and it's a neurophysiological index of spasticity coupled with a decrease in presynaptic activity and a reciprocal inhibition with a reduced facilitation of the fibres of the type '1a'; it's modulated by recurrent inhibitory neurons, under the control of descending inhibitory fibers. Cortical neuromodulation seems to act on the inhibitory components through the spinal cortico-reticular tract, reinforcing the already known changes induced by tDCS [18]. Following the cathodal stimulation carried out in the trial by Del Felice et al., a significant increase in spasticity reduction was observed immediately after intervention with a wide maintenance effect; clinical results are supposed by the decrease in amplitude and an increase in the latency of H reflex [18].

The potential motor evoked (MEPs) investigated [16], showed an increase of amplitude and decrease of latency in the anterior tibialis muscle in the experimental group compared to the control group; these results indicate an increase in cortical excitability consequent by stimulation with physical therapy rehabilitation. Since cortical excitability reflects neural activity, the observed increase in the

experimental group demonstrates that anode stimulation can induce changes in neural activity in the motor cortex; in accordance with the study of Nitsche et al. [7] the increase in cortical excitability is sustained for 90 min after administration.

Conclusion

Despite the encouraging results, in some heterogeneous cases, there is a need to conduct studies with larger sizes of samples; many covariates should be investigated, including lesion extension, type of lesion, and condition of the lesion. There is also a need for a much wider follow-up to clarify as far as possible the long-term effects of neuromodulation. Demographic co-variables may have a role in the age of patients included in the studies, considering the possible presence of geriatric age in comorbidities and small vessel vascular disease. More accurate instrumental investigations could help clarify some aspects of tDCS that are not known yet.

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