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REVIEW

Transcranial Direct Current Stimulation in Conjunction with Mirror Therapy for Upper Extremity Rehabilitation in Chronic Stroke Patients

Penelope VLOTINOU[a], Dimitrios TSIPTSIOS[a], Stella KARATZETZOU[a], Georgios KALOGIROU[a], Eleftherios STEFAS[a], Nikolaos AGGELOUSIS[b], Konstantinos VADIKOLIAS[a]

[a]Neurology Department, Democritus University of Thrace, Alexandroupolis, Greece

[b]Department of Physical Education and Sport Science, Democritus University of Thrace, Komotini, Greece

ABSTRACT

Objective: *Stroke represents a major cause of upper limb motor impairment among stroke survivors, resulting in functional disability and affecting negatively their quality of life. Thus, it is imperative that stroke rehabilitation be efficient. Up to the present, several intervention methods have been proposed in an attempt to improve recovery potential poststroke, transcranial direct current stimulation (tDCS) and mirror therapy (MT) being among them. The aim of this review is to investigate the utility of tDCS administration in conjunction with MT on chronic stroke population.*

Methods: *A literature research of two databases (MEDLINE and Scopus) was conducted in order to identify all relevant studies published between January 1st 2010 and September 30th 2021 that focused on the efficacy of the combined application of tDCS and MT on upper limb rehabilitation among chronic stroke patients.*

Results: *Three studies fulfilled the selection criteria and were included in the present review. Transcranial direct current stimulation application along with MT exhibited statistically significant increases in Box and block test, grip strength, Action research arm test score and Nottingham extended activities of daily living score within the experimental group compared to controls. The timing-dependent interaction effects seem to be of key importance, as sequentially delivered tDCS prior to MT is considered to be more advantageous and time-efficient compared to the concurrent application of tDCS and MT.*

Conclusions: *Application of tDCS in parallel with MT represents a promising neurorehabilitation tool for post-stroke patients regarding upper limb motor performance, movement efficiency and daily function. Future studies are needed in order to clarify whether sequential or concurrent tDCS and MT application is more beneficial.*

Keywords: transcranial direct current stimulation, mirror therapy, stroke, upper extremity, rehabilitation.

Address for correspondence:
Dimitrios Tsiptsios
Neurology Department, Democritus University of Thrace, Alexandroupolis, 68100, Greece
Email: tsiptsios.dimitrios@yahoo.gr

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INTRODUCTION

Stroke represents not only the second leading cause of death, but also the major source of acquired adult disability, as mean stroke incidence has flourished between 76 and 112 per 100,000 population per year worldwide (1). More than half of stroke patients are over 65 years of age (2), highlighting the fact that stroke constitutes an age-related disease with a constantly increasing burden, when taking into account both the world population's growth and extended lifespan (3).

Stroke is usually associated with a great odd of reporting disability, as far as many individual domains are concerned (4-6). For example, during the chronic phase, up to 80% of stroke patients present with upper and lower limb motor impairment, while only 20% exhibit intact hand function (7). Upper limb impairment following stroke commonly refers to a combination of difficulty moving or coordinating the arm, hand or fingers, painful upper limb or hypoesthesia (8, 9). The persistence and disabling character of the aforementioned impairments explain why stroke survivors often exhibit difficulties executing and participating in several activities of daily living (ADL) and subsequent poor quality of life (10).

According to current stroke rehabilitation guidelines, brain remodeling as a result of neuroplasticity, could be facilitated through the implementation of various therapeutic interventions aiming at upper extremity retraining in order to enhance motor and functional recovery (11, 12). The most frequently applied rehabilitation strategies include intensive and task-oriented training movements, repetitive motor training, biofeedback, robotic training, as well as transcranial direct current stimulation (tDCS) and mirror therapy (MT) (13-16).

Non-invasive brain stimulation has been utilized not only as a prognostic tool poststroke (17), but also serving specific therapeutic purposes. Stimulating the human motor cortex, through the delivery of low intensity current to the scalp, tDCS is commonly used in stroke rehabilitation. It has been reported to induce structural neuronal changes, thus modulating the function of neural networks and enhancing the effectiveness of motor learning process. Interestingly, tDCS seems to be of key importance in promoting neuroplasticity. When applied alone, tDCS is proven to be beneficial not only for improving upper limb motor function in chronic stroke patients (18-20), but also for increasing ADL capacity (21, 22). Even though tDCS can be administered alone, it is usually applied in parallel with other neurorehabilitation techniques, in an attempt to positively affect restoration of motor impairment post stroke.

Mirror therapy is a cognitive intervention method which is widely used in clinical and research practice among stroke patients. This motor training technique takes advantage of the visual illusion effect, which provides the impression of a moving paretic upper extremity, thereby enhancing motor performance of the affected side through activation of the mirror neuron system. Mirror neurons are mainly localized in premotor cortex, supplementary motor area, primary somatosensory cortex and inferior parietal cortex. Mirror therapy application, as a stroke rehabilitation approach, has been demonstrated to promote upper limb motor function (23-26) and positively affect restoration of ADL abilities (25, 26). Apart from that, recently published evidence supports the implementation of MT mainly during the subacute phase of stroke, in order to maximize the benefits of the intervention (27). As far as acute and chronic stroke patients are concerned, MT alone is considered to be more effective in facilitating upper limb recovery compared to conventional rehabilitation approach or combined MT with conventional therapy (28).

Mirror therapy has been used in combination with electric stimulation, strength training or transcranial magnetic simulation showing a synergetic effect on hand dexterity improvement (29-31). Mirror therapy implementation along with tDCS after stroke constitutes a scientific field of investigation that attracts the attention of the multidisciplinary rehabilitation team. Thus, the present review aims to explore the efficacy of the combined application of MT and tDCS on upper extremity functional recovery in chronic stroke patients. ❑

MATERIAL AND METHODS

The preferred reporting items for systematic reviews and meta-analyses list (PRISMA check list) was used to guide the present review (32). Our study methods were a priori designed.

Search strategy

Two databases (MEDLINE and Scopus) were selected to carry out the present literature search, which was conducted by one investigator (PV). In order to trace all relevant studies published between January 1st 2010 and September 30th 2021, the following keywords were used: "mirror therapy" AND ["transcranial direct current stimulation" OR "tDCS"] AND "stroke" AND ["upper extremity" OR "upper limb" OR "hand"]. All retrieved articles were also hand searched for any further potential eligible articles. Any disagreement regarding screening, or selection process, was solved by a second investigator (KV) until a consensus was reached.

Selection criteria

Only full-text original articles dealing with adults having suffered a stroke at least six months in advance and published in English language were included. Secondary analyses, reviews, guidelines, meeting summaries, comments, unpublished abstracts or studies conducted in animals were excluded. There was no restriction on study design or sample characteristics.

Data extraction

Data extraction was performed using a predefined data spreadsheet created in Excel. We recorded author, year of publication, number of participants, timing of intervention, study design, intervention duration, intervention frequency, tDCS characteristics (equipment, type of stimulation, procedure, stimulus intensity, sponge electrode area), MT protocol, outcome assessment tools, follow-up period and main results.

Data analysis

No statistical analysis or meta-analysis was performed due to the high heterogeneity among studies. Thus, the data were only descriptively analyzed. ❑

RESULTS

Database searches

Overall, 287 records were retrieved from the database searching. Duplicates and irrelevant studies were excluded; hence, a total of five articles were selected. After screening the full text of the articles, three studies were eligible for inclusion (Figure 1).

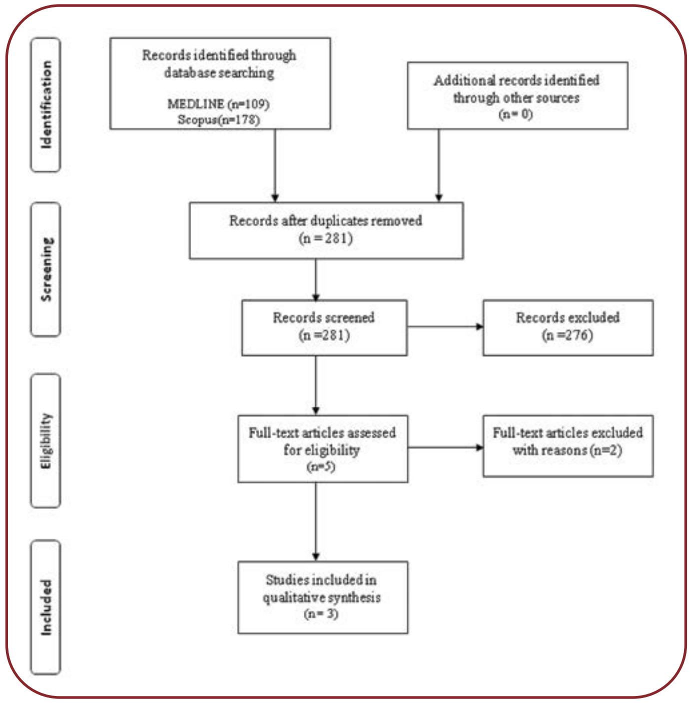

FIGURE 1. Study flow diagram (PRISMA flowchart)

Study characteristics

Three publications fulfilled our inclusion criteria. The reported number of participants who completed all training sessions ranged between 27 and 30 within each study, with an average of around 28.3 participants. Characteristics of included studies are presented in Table 1. ❑

DISCUSSION

Disability resulting from a stroke insult still constitutes a challenging issue concerning stroke survivors, as the identification of optimal neurorehabilitation strategy, aiming to facilitate functional motor recovery poststroke, remains difficult and largely unexplored. Several studies have investigated the effect of tDCS and MT, solely or in combination, on upper limb functional recovery within six months of stroke onset, that is in subacute stroke patients who exhibit the greatest recovery potential (2, 33). The studies included in the present review aimed to explore the impact of combined tDCS and MT implementation on the rehabilitation of a chronic stroke population, that is after the time period that neurological function recovers naturally.

A synergistic approach with post-stroke application of both tDCS and MT seems a quite promising strategy, in order motor recovery of stroke

TABLE 1. Characteristics of the included studies

Authors, country, year of publication	**Cho and Cha, Korea, 2015** (34)	**Jin *et al*, China, 2019** (35)	**Liao *et al*, Taiwan, 2020** (36)
Number of participants	27	30	28
Timing of intervention	≥ six months post-stroke	≥ six months post-stroke	≥ six months post-stroke
Study design	Two groups: **A) experimental group**, n=14: tDCS + MT **B) control group**, n=13 tDCS + same exercise as the experimental group using a mirror that did not show the non-paretic upper extremity	Three groups: **A) SEQ group**, n=10 sequential combination of tDCS with MT **B) CON group**, n=10 concurrent combination of tDCS with MT **C) SHAM group**, n=10 sham tDCS with MT	Three groups: **A) SEQ group**, n=11 sequential combination of tDCS with MT **B) CON group**, n=12 concurrent combination of tDCS with MT **C) SHAM group**, n=11 sham tDCS with MT
Intervention duration	**45 minutes** (20 minutes of tDCS – five minutes of rest – 20 minutes of MT)	**60 minutes** (30 minutes of tDCS – 30 minutes of MT)	**90 minutes** **A) SEQ group:** 20 minutes of tDCS – 20 minutes of tDCS (sham) + MT – 20 minutes of MT – 30 minutes of functional task practice **B) CON group:** 20 minutes of tDCS (sham) – 20 minutes of tDCS +MT – 20 minutes of MT – 30 minutes of functional task practice **C) SHAM group:** 20 minutes of tDCS (sham) – 20 minutes of tDCS (sham) + MT – 20 minutes of MT – 30 minutes of functional task practice
Intervention frequency	Three times per week for six weeks	Five times per week for two weeks	Five times per week for four weeks
tDCS			
tDCS equipment	Phoresor II Auto model PM 700, IOMED, Salt Lake City, USA	Soterix Medical 1×1 tDCS Low-Intensity Stimulator, New York, USA	NeuroConn GmbH, Ilmenau, Germany
Type of stimulation	Anodal and cathodal	Anodal and cathodal	Anodal
tDCS procedure	The anode electrode was attached to C3 and C4 according to the International 10/20 system, the primary motor cortex (M1), while the cathode electrode was attached to the contralesional supraorbital area	The cathode electrode was placed over the primary motor cortex (M1) of the contralesional hemisphere (C3 position, according to the 10/20 EEG system) and the anode electrode was placed above the ipsilateral M1 position.	The anode electrode was attached to C3 and C4 according to the International 10/20 system, the primary motor cortex (M1), while the cathode electrode was attached to the contralesional supraorbital area
Stimulus intensity	2 mA	1 mA	2 mA
Sponge electrode area	24 cm^2	35 cm^2	35 cm^2
MT			
MT protocol	The paretic hand was hidden behind a 35×35 cm mirror, and the non-paretic hand was put in front of the mirror. Subjects looked at the upper extremity of the non-paretic side reflected in the mirror and observed the	Five table-top tasks, customized accordingly to each patient's functional level and based on the seven functional levels of the FTHUE (37) were utilized. The participants were	MT consisting of: (1) intransitive movements, including distal and proximal arm/hand movements such as wrist extension-flexion, forearm pronation-supination and elbow flexion-extension, and (2) transitive movements, such as placing pegs in holes or flipping a card

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	movement. The MT program consisted of pronation, supination, flexion, and extension of both wrists, flexion and extension of the fingers, and flexion and extension of the elbows. One set consists of 20 repetitions of each motion. Subjects perform 10 sets and rest for two minutes between sets.	instructed to perform as many trials as possible in each session, with a maximum of 30 trials *per* task, giving a total of 150 trials *per* session.	
Outcomes			
Outcome assessment tools	▪ BBT (38) ▪ JAMAR hand dynamometer (Sammons Preston Rolyan, Illinois, USA) ▪ Jebsen-Taylor test (39) ▪ FMA-UE subscore (40)	▪ BBT (41) ▪ FMA-UE subscore (40) ▪ ARAT (42)	▪ NEADL scale (43) ▪ FMA-UE (40) ▪ Movement kinematic assessment for evaluating upper extremity motor control utilizing a seven-camera motion analysis system (VICON MX; Oxford Metrics Inc., Oxford, England)
Main results	A statistically significant difference between the two groups was found, as far as the BBT and grip strength are concerned, indicating that the experimental group demonstrated a greater improvement of manual dexterity and hand grip strength the experimental group showed more significant increases in the BBT and grip strength than the control group. Both groups showed amelioration of hand functionality impairment	A statistically significant difference was detected in the ARAT score in favor of concurrent-tDCS group over both prior-tDCS and sham-tDCS groups at post-intervention. However, such a significant improvement was not identified across the three groups regarding the FMA-UE and BBT scores	Statistically significant improvement of daily function was reported in the SEQ group compared to CON and SHAM groups, indicating a timing-dependent effect of tDCS with MT as far as ADL capacity is concerned Upper limb motor control was significantly enhanced within the SEQ group more than the other two groups No additional benefits of tDCS with MT were found on speeding up motor function
Limitations	1. Limited number of participants 2. No control over therapy duration 3. No subjects' separation based on functional performance level 4. Patients conducted only simple tasks	1. Small number of tDCS + MT sessions 2. Low stimulus intensity of tDCS 3. Participants' heterogeneity in terms of stroke location and severity 4. The motor priming effect of MT itself is considered to be beneficial for all groups, independently of tDCS time of application 5. Short duration of follow-up period	1. Participants with only mild to moderate degree of motor impairment 2. Absence of neurophysiological and neuroimaging outcomes 3. Without follow up assessment 4. Individualization of functional task training for each patient 5. Differential improvements between the groups did not reach a level of statistical significance due to small sample size

tDCS-transcranial direct current stimulation, MT=mirror therapy, n=number, seq=sequential, con=concurrent, FTHUE=Functional test for the hemiplegic upper extremity, BBT=Box and block test, FMA-UE=Fugl-Meyer assessment-upper extremity subscore, ARAT=Action research arm test, NEADL=Nottingham extended activities of daily living scale

patients to be further enhanced. Cho and Cha (34) investigated the influence of sequentially combined tDCS with MT on chronic stroke patients compared to tDCS administration in conjunction with motor training using a mirror that did not reflect the non-paretic upper extremity.

The researchers reported statistically significant increases in the Box and block test (BBT) and grip strength within the experimental group more that those found in the control group, thus eliciting a link between the sequential use of tDCS and MT and the enhancement of manual dexterity and hand grip strength poststroke. The positive impact of the combined approach on functional motor recovery of chronic stroke patients was attributed to the role played by MT in motivating participants as well as the effect of tDCS on the function of the neuronal circuit in the motor cortex.

The effects of applying tDCS in parallel with MT in stroke survivors may not be just additive, implying that the interventions' order of implementation could affect overall the rehabilitation process. With regards to the timing-dependent interaction effect, Jin *et al* (35) conducted a study and examined 30 chronic stroke patients who had been allocated to three different groups, depending on the intervention flow. Researchers delivered tDCS either prior or concurrently with movement practice of MT or not at all (sham-tDCS), in order to investigate how the timing would influence treatment effects poststroke. Their results revealed a greater improvement in the Action research arm test (ARAT) score when tDCS was administered simultaneously with MT compared to when tDCS was applied prior to MT or the sham condition, thus identifying a motor priming effect of concurrent-tDCS in conjunction with MT, as far as upper limb recovery is concerned. Although participants of the concurrent-tDCS group scored higher in the Fugl-Meyer assessment-upper extremity (FMA-UE) subscore and BBT post-intervention than the other two intervention groups, these differences did not achieve a significance level. The delivery of tDCS coupled with MT at the same time was found to be beneficial for restoration of motor performance after stroke, but the aforementioned approach did not yield to similar benefits regarding all reported outcomes.

The impact of timing-dependent effect of tDCS and MT in terms of motor performance, daily function, as well as upper extremity motor control was also investigated by Liao *et al* (36). Adult individuals with chronic stroke were involved in this study and assigned to three intervention groups, which were differentiated by the timing of tDCS application in relation to MT. As far as the clinical and kinematic outcomes were concerned, the researchers concluded that sequentially applied tDCS with MT was followed by a statistically significant increase in the Nottingham extended activities of daily living (NEADL) scale score, more than in the concurrent- or sham-tDCS group, thus indicating that the order of motor priming and training may influence restoration of ADL capacity. Similar results were not found with regard to FMA-UE scale, as motor impairment was recovered to a same degree between different intervention groups, thereby showing that the implementation of tDCS either simultaneously or prior to MT was not coupled with additional benefits on motor function. With respect to arm kinematics, it was demonstrated that the timing of tDCS could play a role in improving spatial and temporal upper limb motor control, as participants in the concurrent-tDCS groups were able to move their hand and arm more efficiently compared to the other groups.

Overall, the results of the present review should be considered as conflicting. Cho and Cha (34) found a significant enhancement in manual dexterity and grip strength when applying tDCS prior to MT than motor practice without mirror reflection, thus highlighting the fact that a sequential combination of tDCS with MT was able to promote motor recovery of upper limb during the chronic phase of stroke. By contrast, Liao *et al* (36) could not elicit a link between the use of tDCS in parallel with MT and motor function, as far as all intervention groups were concerned. With respect to ADL abilities and upper limb motor control, the researchers concluded that timing proved of key importance, as the sequential-tDCS group exhibited greater functional independence and movement efficiency than the concurrent-tDCS group or the sham condition. The outcomes of the study conducted by Jin *et al* (35) were inconsistent with those of the aforementioned studies, as the delivery of tDCS during the movement practice of MT was followed by benefits on motor recovery, only though regarding the ARAT score, but not also the other investigated clinical outcomes.

The heterogeneity of the included studies in terms of intervention protocols and outcome measures could be responsible for the differential results among studies. Cho and Cha (34) administered tDCS of 2 mA for 20 minutes, three times per week, for six weeks, while Jin *et al* (35) delivered low intensity tDCS of 1 mA for 30 minutes, in five sessions per weeks, across two weeks. Apart from that in the study of Liao *et al* (36), participants' motor cortex was stimulated with anodal only tDCS of 2 mA that lasted 20 minutes, five days per week, for four consecutive weeks. Moreover, the applied MT protocol had variations between the three studies regarding the movement practice and performed upper limb tasks. As far as the outcome measures were concerned, both Cho and Cha (34) and Jin *et al* (35) evaluated the effects of combined application of tDCS with MT on motor function using only clinical measurements, while Liao *et al* (36) assessed the impact of neurorehabilitation interventions on functional independence and upper limb motor control, utilizing outcomes measures related to daily activities and movement kinematics. Several limitations of the included studies are also mentioned in Table 1. Future studies should address them, in order to optimize the outcomes and identify the most beneficial combination neurorehabilitation strategy for improving poststroke recovery. ❑

CONCLUSIONS

Our findings indicate that the application of tDCS in conjunction with MT constitutes a promising approach, which is expected to enhance upper limb rehabilitation efficiency even in chronic stroke population. Although the results regarding the timing-dependent interaction effect of tDCS with MT on stroke patients' recovery seem rather controversial, sequentially delivered tDCS prior to MT is considered to be more advantageous and time-efficient compared to concurrent application of tDCS and MT. Additional studies on the impact of the aforementioned neurorehabilitation approach are recommended, in order to identify the optimal combination strategy and provide further insight on the relationship between application of tDCS in parallel with MT and motor recovery in stroke patients. ❑

Conflicts of interest: none declared.

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