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Timing-dependent interaction effects of tDCS with mirror therapy on upper extremity motor recovery in patients with chronic stroke: A randomized controlled pilot study

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ABSTRACT

This study was a randomized, controlled pilot trial to investigate the timing-dependent interaction effects of dual transcranial direct current stimulation (tDCS) in mirror therapy (MT) for hemiplegic upper extremity in patients with chronic stroke. Thirty patients with chronic stroke were randomly assigned to three groups: tDCS applied before MT (prior-tDCS group), tDCS applied during MT (concurrent-tDCS group), and sham tDCS applied randomly prior to or concurrent with MT (sham-tDCS group). Dual tDCS at 1 mA was applied bilaterally over the ipsilesional M1 (anodal electrode) and the contralesional M1 (cathodal electrode) for 30 min. The intervention was delivered five days per week for two weeks. Upper extremity motor performance was measured using the Fugl-Meyer Assessment-Upper Extremity (FMA-UE), the Action Research Arm Test (ARAT), and the Box and Block Test (BBT). Assessments were administered at baseline, post-intervention, and two weeks follow-up. The results indicated that concurrent-tDCS group showed significant improvements in the ARAT in relation to the prior-tDCS group and sham-tDCS group at post-intervention. Besides, a trend toward greater improvement was also found in the FMA-UE for the concurrent-tDCS group. However, no statistically significant difference in the FMA-UE and BBT was identified among the three groups at either post-intervention or follow-up. The concurrent-tDCS seems to be more advantageous and time-efficient in the context of clinical trials combining with MT. The timing-dependent interaction factor of tDCS to facilitate motor recovery should be considered in future clinical application.

1. Introduction

Neuroplasticity, which refers to the ability to rebuild anatomical and functional connectivity in order to react to external stimuli, is currently underpinning post-stroke functional recovery [1]. Researchers have explored hybrid or a combination of different modalities as possible ways to facilitate motor recovery after a stroke. Priming has been defined as a type of implicit learning wherein a change in behavior is induced by a stimulus [2]. In rehabilitation, motor priming has been reported in motor skill learning in order to facilitate the sensorimotor system to be more ready for sequential motor treatment, consequently enhancing behavioral outcomes [3]. Priming can be classified into prior or concurrent priming in terms of the time of application, and stimulation-based, mental based, movement based, pharmacological based and sensory-based in terms of the modalities used [2].

Transcranial direct current stimulation (tDCS) is commonly used as a form of stimulation-based priming. It is a safe and noninvasive therapeutic approach that causes a shift in membrane potential threshold which increases the probability of neurons in the cerebral cortex firing. The idea of tDCS is that it boosts subthreshold neuronal action potentials, thus may achieve stronger neurons firing than would occur without administering tDCS. The tDCS stimulator sends a low-level current from the anodal electrode to the cathodal electrode via surface electrodes attached to the scalp. With the application of anodal tDCS, the brain activity under the anodal electrode is likely to increase, whereas under the electrode in cathodal tDCS is likely to be inhibited [4,5]. The reasoning behind using tDCS for motor recovery in stroke is based on the interhemispheric competition theory that hemiplegia, due to a stroke, can lead to an imbalance between the two hemispheres, followed by the inhibition of the affected cerebral cortex and the excitation of the less affected hemisphere

Abbreviations: ARAT, Action Research Arm Test; BBT, Box and Block Test; FMA-UE, Fugl-Meyer Assessment-Upper Extremity; FTHUE, Functional Test for the Hemiplegic Upper Extremity; LTD, Long-term depression; LTP, Long-term potentiation; MAS, Modified Ashworth Scale; MCID, Minimal clinically important differences; MMSE, Mini-Mental State Examination; MT, Mirror therapy; tDCS, Transcranial direct current stimulation

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[4,5]. Accordingly, tDCS can speed up motor recovery of the paretic upper limb, likely by rebalancing abnormal interhemispheric interactions, enhancing ipsilesional M1 excitability, reducing contralateral excitability, or doing both [6]. There have been two recent meta-analyses regarding the effects of rTMS and tDCS on hemiplegic upper limb recovery after stroke [4,7]. All three stimulation paradigms, including anodal, cathodal, and dual (applied bihemispherically) tDCS, have shown short-term benefits for chronic stroke patients with mild to moderate upper limb impairment [8].

Three studies have used tDCS as prior motor priming [9–11]. In those studies, one of them compared the three groups (anodal vs cathodal vs sham group) [11], and the other two only compared the anodal [10] or cathodal [9] groups with a sham group intervention, which was performed by using cathodal stimulation on the unaffected hemisphere or anodal electrode on the affected side or both of them together with 1.5–2 mA of electric intensity and a duration of 10–25 min per session. All the studies used daily sessions and the number of total sessions varied from two to 10 sessions, according to different study designs. Four [12–15] studies chose tDCS as concurrent priming combined with other treatments, two of them [13,14] had a three-group design trial which consisted of an anodal group, a cathodal group, and a sham group. One study [15] only compared a cathodal group with a sham group. Another study used dual tDCS stimulation (with the anode over the affected side M1 and the cathode over the unaffected side M1) to compare results with a sham group [12].

tDCS can be combined with explicit motor training to enhance the effectiveness of motor learning. Two studies [13,15] combined tDCS with virtual reality, and one study combined tDCS with robot-assisted arm training. The dual tDCS study combined tDCS with constraint-induced movement therapy (CIMT) [12]. Mirror therapy (MT) is a widely used motor training method and has also been demonstrated to be significantly beneficial for post-stroke upper limb motor recovery with a moderate effect size [16]. During the treatment, a mirror is placed in the subject's midsagittal plane. With the affected side behind the mirror, the subject can only see the unaffected side and its reflection in the mirror, so that the affected side appears to be performing the same movement [17]. This combination of MT and tDCS has been demonstrated to be useful in the motor recovery of hemiplegic upper limbs in patients with chronic stroke [18].

Recently, increasing evidence has demonstrated that the order of motor priming and training may influence the interaction effect between tDCS and behavioral tasks [1,2,19]. Given that most relevant studies were conducted in healthy populations and that different forms of tDCS have been used in motor priming, we would like to investigate the timing-dependent interaction effect of tDCS with MT in the stroke population. We hypothesize that dual tDCS applied simultaneously with MT would lead to a greater enhancement in motor performance than that of tDCS applied prior to MT, as well as sham tDCS applied before or simultaneously with MT.

2. Methods

2.1. Participants

Thirty participants with stroke were recruited from self-help stroke organizations in Hong Kong from January 2018 to May 2018, based on convenience sampling. Our study was performed in accordance with the principles of the Declaration of Helsinki and ethical approval was sought from the human ethics committee of the Hong Kong Polytechnic University before implementation (reference no. HSEARS20180118006). The study was retrospectively registered in the Chinese Clinical Trial Registry (no. ChiCTR180002008).

Only participants who had given informed written consent were included in the study. Participants were assessed for eligibility based on the following inclusion criteria: 1) adults (aged ≥ 18 years old) who had experienced their first stroke more than six months ago; 2) upper

extremity impairment \geq second level in the Functional Test for the Hemiparetic Upper Extremity (FTHUE) [20]; 3) medically stable; 4) Mini-Mental State Examination (MMSE) score ≥ 21 , to ensure the participant could understand the instructions and give consent; 5) not participating in other clinical, drug, or research studies at the same time; and 6) passed the safety screening for tDCS. Those who had severe health conditions that required intensive medical care, such as heart failure, pneumonia, a poor nutritional state, or contraindications of tDCS, such as a cardiac pacemaker, cancer, bleeding tendencies, pregnancy, metal implants, a history of seizures, etc., were excluded from the study.

2.2. Study design

A randomized, controlled pilot trial was conducted, wherein participants admitted consecutively were randomly allocated to one of the three training groups: 1) dual tDCS applied before MT (prior-tDCS group); 2) dual tDCS applied simultaneously with MT (concurrent-tDCS group); and 3) dual sham-tDCS applied before or simultaneously with MT (sham-tDCS group). Group allocations were sealed in opaque envelopes, which were kept by a third-party researcher. Once participants were enrolled, the researcher opened the envelopes and informed the study investigators of the group allocation.

2.3. Interventions

2.3.1. Transcranial direct current stimulation (tDCS)

The protocols of tDCS vary in the literature in terms of duration of stimulation, intensity, and density of current delivered. Some studies have reported that the duration typically ranges from 10 to 30 min [21–23] and even a 10-min duration could present sufficient effects to elicit prolonged effects for more than one hour after the session [24]. In terms of density, the majority of studies have applied tDCS with a current density of 1 mA/35 or 25 cm², without any reports of severe adverse effects [25]. Previous studies have demonstrated that patients who received a current intensity over 2 mA were more likely to perceive pain [26].

In this study, we used the Soterix Medical 1 × 1 tDCS Low-Intensity Stimulator, and a 1 mA tDCS current was delivered through two 35 cm × 35 cm saline-soaked surface sponge electrodes for 30 min, 5 days per week, for 2 weeks. With references to previous studies and recommendations for tDCS studies in stroke [27,28], the cathodal electrode was placed over the primary motor cortex (M1) of the contralateral hemisphere (C3 position, according to the 10/20 EEG system), and with the anodal electrode placed above the ipsilateral M1 position. A head band was used to attach the electrodes. Initially, the current ramped up gradually to 1 mA in 30 s., in order to avoid adverse sensations. The 30-min training duration did not include the 30 s. ramp up time at the start of stimulation and an approximately 30 s. ramp down time at the end of stimulation. With regard to the sham condition, the sham button of the device was switched on so that only an approximately 30 s. ramp up and an approximately 30 s. ramp down was delivered. The experimental setup can be found in Fig. 1.

2.3.2. Mirror therapy (MT)

The movement practice for each group involved five table-top tasks. The participants were 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. Exercises were customized and based on the seven functional levels of the Functional Test for the Hemiplegic Upper Extremity (FTHUE) [20]. Examples of customized tasks are shown in the Appendix. The FTHUE was developed originally according to Brunnstrom's developmental stages of stroke recovery and has been validated and used extensively for stratification of hemiplegic upper extremities in recent studies [21].

During each session, participants in the prior-tDCS group received 30 min of stimulation prior to 30 min of MT training. In the concurrent-tDCS condition, tDCS was applied for 30 min at the same time as the

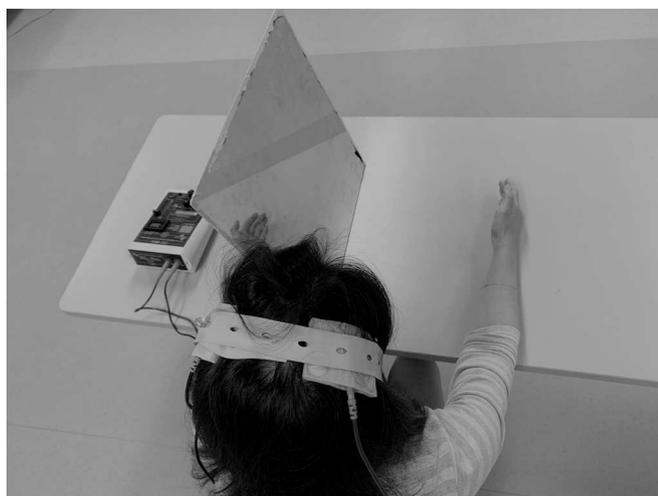


Fig. 1. Experimental setup of mirror therapy and tDCS stimulation.

30 min of MT training. In the sham-tDCS group, in order to eliminate the effect of favoring either prior-tDCS or concurrent-tDCS conditions as well as providing similar dosage of MT in the sham, participants performed tasks with sham stimulation randomly prior to or concurrent with MT. The intervention was delivered five days per week for two weeks.

2.4. Outcome measurements

The primary outcome was the motor function of the hemiplegic upper extremity. Three motor scales were used, including the Fugl-Meyer Assessment-Upper Extremity Subscore (FMA-UE) [22], the Action Research Arm Test (ARAT) [29], and the Box and Block Test (BBT) [30]. All of the assessments were evaluated before the first session (T0), at post-intervention (T1), and at the two-week follow-up (T2) by investigators who had received standard training.

The FMA is a classic motor measurement scale designed for the hemiplegic upper extremity. The FMA contains five domains and has better psychometric properties than most other assessments designed for clinical trials [31]. In the present study, only the upper extremity subscale (FMA-UE) was used. It includes 33 items, with each item rated

from 0 to 2 (0 = cannot perform, 1 = can partially perform, and 2 = can fully perform). The FMA-UE scores range from 0 to 66. The ARAT is commonly used to measure upper extremity motor function after stroke, in a laboratory setting; it consists of four subtests: grasp, grip, pinch, and gross motor. Evidence demonstrates that the ARAT possesses satisfactory psychometric properties when used with stroke patients with mild to moderate motor severity [29]. The BBT counts the number of blocks that can be transported by participants from one compartment of a box to another compartment within one minute. It is a measure of gross manual dexterity and demonstrates good inter-rater and test-retest reliability [30].

2.5. Statistical analysis

An intention-to-treat analysis was applied to deal with the missing data. Descriptive statistics were expressed as means and standard deviations (SDs) (Table 1). Due to the small sample size, non-parametric statistical methods were adopted. The baseline of the clinical and demographic data was compared across three groups using Fisher's exact test or the Kruskal-Wallis test for the categorical or continuous data, respectively. The Friedman Test was used to compare the within-group differences at T0, T1, and T2 (Table 2). Between-group differences for the Gain Score 1 (T1-T0) and Gain Score 2 (T2-T0) were evaluated by the Kruskal-Wallis Test (Table 2). The statistical significance level was set at 0.05. Significance values for post-hoc tests have been adjusted by the Bonferroni correction, so that $p = .05/n$, where n = number of variables; therefore, p was set at 0.017 in the between-group comparison. Minimal clinically important differences (MCID) were used to compare the results of the present study if significant differences were found. All statistics were calculated using SPSS version 20.

3. Results

Thirty patients were recruited, with 10 allocated to the prior-tDCS group, 10 to the concurrent-tDCS group, and 10 to the sham-tDCS group. The participants' flow charts can be found in Fig. 2. Two participants dropped out during the study, one from the prior-tDCS group and another from the sham-tDCS group. None of the patients reported discomfort or severe side effects.

Demographics and outcomes are summarized in Table 1. The

Table 1
Demographics and baseline characteristics.

Variable	Groups ^c			P*
	Group 1 (n = 10)	Group 2 (n = 10)	Group 3 (n = 10)	
Age (years)*	59.00 (9.80)	58.70 (7.92)	57.50 (7.08)	0.753 ^b
Gender (female/male)	2/8	3/7	1/9	0.847 ^a
Stroke onset (months)*	19.44 (8.25)	20.46 (11.13)	22.16 (8.15)	0.747 ^b
Hemiparetic side (right/left)	4/6	8/2	7/3	0.249 ^a
Stroke type (ischemic/hemorrhagic)	8/2	4/6	8/2	0.668 ^a
Usual care (yes/no)	9/1	7/3	6/4	0.450 ^a
FMA-UE*	52.70 (18.56)	45.80 (15.97)	49.30 (18.14)	0.426 ^b
BBT*	28.60 (16.48)	19.00 (17.37)	22.80 (20.32)	0.570 ^b
ARAT*	42.90 (22.02)	33.10 (18.86)	35.00 (22.18)	0.348 ^b
FTHUE*	5.90 (2.08)	5.20 (1.81)	5.10 (2.18)	0.603 ^b
Higher functioning (levels 5–7)	8	6	6	NA
Lower functioning (levels 1–4)	2	4	4	NA
MAS_arm*	0.65 (0.58)	0.90 (0.70)	0.95 (0.72)	0.493 ^b
MAS_hand*	0.45 (0.60)	0.65 (0.71)	0.55 (0.90)	0.813 ^b

*Data expressed as means (SDs).

* $P \leq .05$; tDCS = transcranial direct current stimulation; MT = Mirror Therapy; FMA-UE = Fugl-Meyer Assessment-Upper Extremity Subscore; BBT = Box and Block Test; ARAT = Action Research Arm Test; FTHUE = Functional Test for the Hemiplegic Upper Extremity; MAS = Modified Ashworth Scale.

^a Fisher's exact test was used to compare proportions for categorical variables.

^b The Kruskal-Wallis test was used to compare means.

^c Group 1 = prior-tDCS group, Group 2 = concurrent-tDCS group, Group 3 = sham-tDCS group.

Table 2
Within-group (pretest, posttest, and follow-up) and between-group comparisons (Group 1, Group 2, and Group 3).

Variable	Group 1 (n = 10)				Group 2 (n = 10)				Group 3 (n = 10)				p ^c	Multiple comparison ^d							
	T0 Mean (SD)	T1 Mean (SD)	T2 Mean (SD)	p ^a	Gain Score 1 Mean (SD)	Gain Score 2 Mean (SD)	T0 Mean (SD)	T1 Mean (SD)	T2 Mean (SD)	p ^a	Gain Score 1 Mean (SD)	Gain Score 2 Mean (SD)			T0 Mean (SD)	T1 Mean (SD)	T2 Mean (SD)	p ^a	Gain Score 1 Mean (SD)	Gain Score 2 Mean (SD)	
FMA-UE	52.70 (18.56)	54.10 (18.02)	53.00 (18.51)	0.047*	1.40 (2.07)	0.30 (1.77)	45.80 (15.97)	49.10 (15.61) [#]	48.60 (16.10)	0.007*	3.30 (3.27)	2.80 (3.61)	49.30 (18.14)	50.50 (17.30)	50.20 (18.33)	0.157	1.20 (1.87)	0.90 (1.79)	0.154	0.238	
ARAT	42.90 (22.02)	44.20 (22.43)	44.40 (21.38)	0.003*	1.30 (1.89)	1.50 (1.96)	33.10 (18.86)	39.70 (18.19) [#]	38.30 (18.01) [#]	0.001*	6.60 (6.43)	5.20 (6.63)	35.00 (22.18)	36.30 (22.71)	36.00 (22.53)	0.015*	1.30 (1.49)	1.00 (1.15)	0.010*	0.172	1, 2, 2, 3
BBT	28.60 (16.48)	31.90 (18.35)	32.60 (17.98)	0.004*	3.30 (3.27)	4.00 (5.06)	19.00 (17.37)	24.60 (19.30) [#]	23.40 (18.66)	0.007*	5.60 (6.31)	4.40 (4.03)	22.80 (20.32)	26.20 (23.82)	25.30 (22.69)	0.276	3.40 (6.26)	2.50 (5.62)	0.426	0.278	

^a The Friedman Test was used to compare within-group differences.
^b The Kruskal-Wallis test was used to compare between-group differences for Gain Score 1 (T1-T0).
^c The Kruskal-Wallis test was used to compare between-group differences for Gain Score 2 (T2-T0).
^d Post hoc analysis had not been carried out, as there was no overall significant difference among the three groups; Group 1 = prior-tDCS group, Group 2 = concurrent-tDCS group, Group 3 = sham-tDCS group.
^{*} p ≤ .05.
[#] Adjusted p ≤ .05 compared with T0; FMA-UE = Fugl-Meyer Assessment-Upper Extremity Subscore; BBT = Box and Block Test; ARAT = Action Research Arm Test.

distributions of age, gender, stroke onset, paralyzed side, types of stroke, usual care (which refers to regular clinical rehabilitation training), and the baselines of outcomes were comparable across groups. Regarding the within-group comparison, there was statistically significant improvement in the ARAT when tDCS was applied concurrently at both post-intervention (P = .002) and follow-up (P = .030), whereas a significant increase in the FMA-UE (P = .022) and the BBT (P = .042) were only found at post-intervention in the concurrent-tDCS condition (Table 2). Compared with the MCID for the FMA-UE in individuals with chronic stroke (MCID = 5.25) [32] and that for the ARAT (MCID = 5.7) [33] and the BBT (MCID = 6) [34], none of the gain scores achieved a clinical significance level. In regard to the between-group comparison, overall significant difference was found in Gain Score 1 in the ARAT (p = .010). The post-hoc comparison showed that there was significant improvement in the ARAT between the concurrent-tDCS group and the prior-tDCS group (p = .022), and between the concurrent-tDCS group and the sham-tDCS group (p = .031) (Table 2). Although the gain scores in the FMA-UE were higher for the concurrent-tDCS group than the prior-tDCS and sham groups, no statistically significant difference could be seen across the three groups in regard to the gain scores for the FMA-UE and the BBT (Fig. 3).

4. Discussion

This study aimed to explore the time-dependent effect of dual tDCS with MT on the motor recovery of upper limbs in individuals with chronic stroke, compared to a combination of sham-tDCS and MT. The results demonstrated a significantly greater improvement in the ARAT at post-intervention when tDCS was applied concurrently with MT than prior to MT, as well as the sham condition. The results might imply that there was a motor priming effect of concurrent-tDCS in combination with MT when compared to the sham condition.

Our results regarding the robust improvements in behavioral measures in the concurrent tDCS application are partially in line with previous studies [1,19]. The results might be attributed to the way in which motor learning in human M1 was associated with an increase in the synaptic strength in the form of long-term potentiation (LTP) like or long-term depression (LTD) like changes [35–37]. For motor priming, the underlying theory is that priming could increase neural activity and facilitate the subsequent induction of LTP or LTD-like plasticity, which would induce a change in the process of motor learning [38]. Thus, our results imply that the application of tDCS over M1 during motor practice is more likely to facilitate corticospinal excitability and consequently enhance the effects of the accompanying training. A study using a similar paradigm regarding lower limbs found that the concurrent application of tDCS resulted in a trend toward greater increases in corticospinal excitability (recorded by motor-evoked potential from the Tibialis muscle) than tDCS applied prior to motor training [1]. This superiority resulting from the concurrent-tDCS protocol may be explained by the Gating theory, which can be induced instantaneously from tDCS with motor practice and occurs by cortical disinhibition (i.e., anodal to the ipsilateral hemisphere and cathodal to the contralesional hemisphere). Any intervention that leads to an acute disinhibition of intracortical inhibitory circuits may gate the effects of a conditioning protocol [38], consequently enhancing the effectiveness of MT when it is applied simultaneously. In contrast, compared to the sham condition, our results regarding tDCS applied before MT did not show any significant improvement on motor learning, which is consistent with several previous studies [1,10,39]. When tDCS is used in conjunction with another intervention successively, it is likely that the time course between the priming stimulation and motor training is considered as essential to the magnitude of boosting neuronal action potentials to induce plasticity [40].

When comparing the two-week follow-up results among the three groups, no significant difference in any of the three outcome measurements was observed. These findings are opposed to some previous studies. According to a recent review of the long-term maintenance

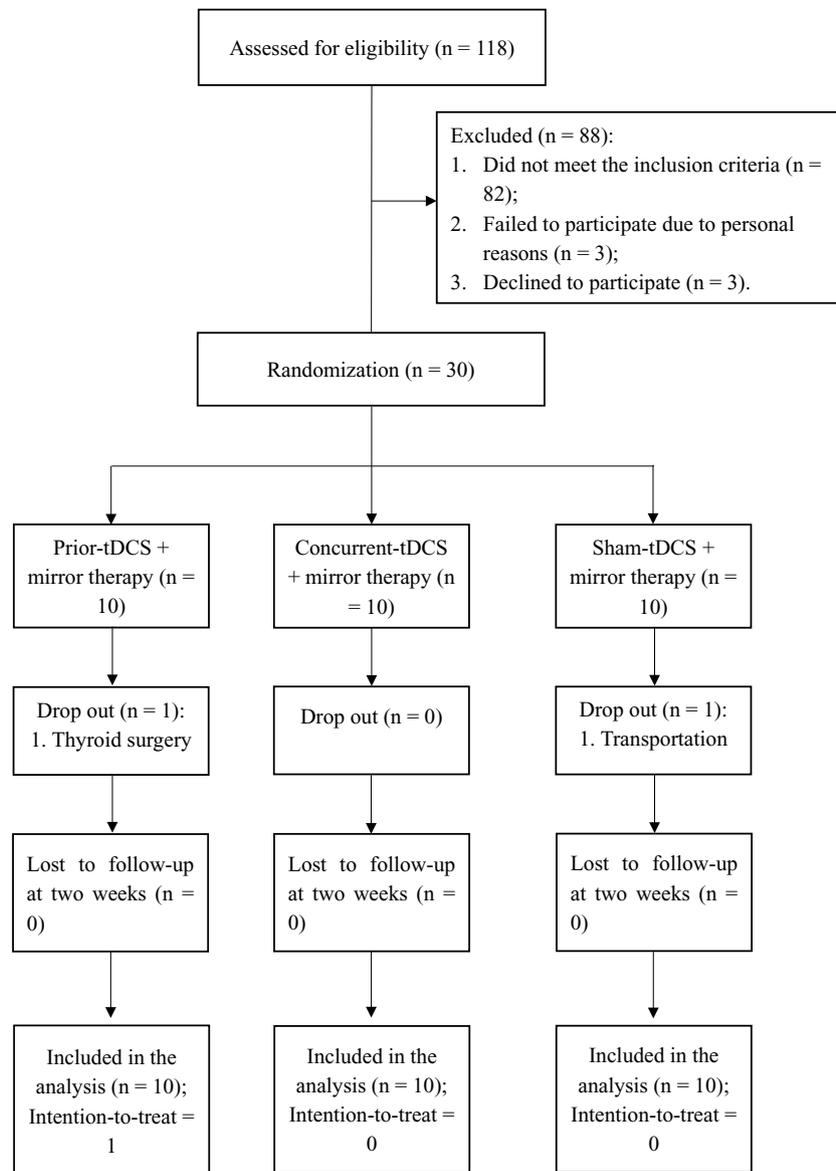


Fig. 2. CONSORT diagram of subjects throughout the study.

effect of tDCS in facilitating motor learning post-stroke [4], dual (bi-hemispheric) tDCS could induce significant long-term motor learning retention in chronic stroke patients. There are three possible reasons for our discrepant results. The first is that the priming effect of tDCS could not be adequate to lead to acquired motor skills improvement, compared with sham tDCS. In the present study, improvements from the short intervention period of tDCS (i.e., 10 sessions, with 30 min per session) were relatively limited. The second reason is related to the heterogeneity and chronicity of recruited patients with stroke. As demonstrated in Table 1, some patients received extra rehabilitation training at varied intensities and recovery was slow due to chronic stroke.

Several limitations were identified in the present study. First, although significant pre-post improvements were found in the FMA-UE, ARAT, and BBT in the prior-tDCS and concurrent-tDCS groups at post-intervention, compared with the MCID for the FMA-UE in individuals with chronic stroke (MCID = 5.25) [32] and that for the ARAT (MCID = 5.7) [33] for the BBT (MCID = 6) [34], none of the gain scores demonstrated clinical significance due to the intervention. A

possible explanation for this could rely on the comparatively small quantity of total intervention sessions. A previous study that explored the interaction effect on chronic patients of tDCS, accompanied by MT and delivered over 18 sessions across six weeks, showed significantly positive results [18]. Another study that focused on the effectiveness of the combination of tDCS and virtual reality in chronic stroke patients conducted 15 sessions, which resulted in > 50% of the participants achieving the MCID in the experimental group [41]. Future studies may increase the number of intervention sessions to achieve more persuasive results. Second, although the current intensity of using 1 mA was referenced in another study of dual tDCS [6], it could be too low and might be for this reason we did not detect any persistent effects of the treatment at the follow-up visit. Third, our patients were quite varied in terms of stroke characteristics, whereas stroke severity and location were suggested as potential covariates to modify the effects of a combination protocol of tDCS and explicit motor training [42]. Moreover, MT itself could be considered as a movement-based priming that would induce a positive effect to motor learning and could be beneficial to all groups. The follow-up

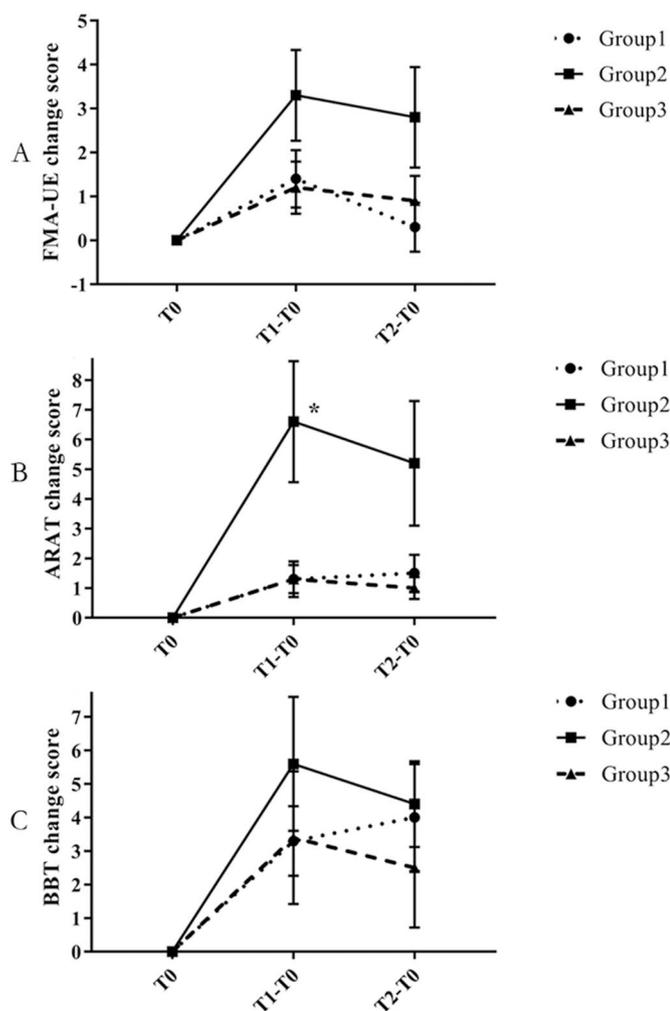


Fig. 3. T1-T0, T2-T0 change scores for the FMA-UE, ARAT, BBT among three groups. Note: Error bars represent (SEM). * $P < .05$ when compared with the sham group; Group 1 = prior-tDCS group, Group 2 = concurrent-tDCS group, Group 3 = sham-tDCS group.

evaluation after 2 weeks was also relatively short in duration. Future studies could be to recruit more subjects and reduce heterogeneity when recruiting cases, limit the age and the FTHUE level to control the

Appendix A. Customary mirror therapy training tasks for the upper extremity

Corresponding levels in FTHUE-HK	Principles of movement	Examples of tasks recommended ^a
Two	1. Passive range of motion movement; 2. Balance the strength of flexors and extensors	- Passive shoulder flexion and extension with elbow extension - Passive elbow exercise with forearm supported on table - Passive wrist flexion and extension with forearm pronation and supported on table
Three	3. Improve the control of shoulder and elbow 4. Facilitate functional synergy	- Passive forearm pronation and supination - Shoulder circular motion - Elbow extension and flexion - Passive forearm pronation and active-assistive supination with elbow flexion at 90° - Passive wrist flexion and active extension with forearm supination
Four	1. Isolated limb segments control training 2. Grasp and release training	- Passive finger flexion and extension - Shoulder flexion at 90° with elbow in full extension and shoulder extension with elbow flexion - Active/active-assistive forearm pronation and supination - Wrist circumduction with elbow flexion or extension - Grasp and release exercise

potential covariates.

5. Conclusion

This study investigated the timing-dependent interaction effects of tDCS in conjunction with MT in the chronic stroke population. We found that the priming effect of tDCS was important to facilitate motor recovery in MT. Significant improvements after concurrent-tDCS and MT in only one motor function test were found when compared with prior-tDCS or sham-tDCS and MT but could not be seen in other outcomes. The concurrent-tDCS seems to be more advantageous and time-efficient in the context of clinical trials combining with other kinds of motor rehabilitation training which should be considered in future application.

Consent for publication

None.

Availability of data and material

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

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Authors' contributions

Conceptualization: FNKK, ZZ, JM. Data collection, analysis and interpretation: JM, ZZ, BZ. Drafting of manuscript: FNKK, JM, ZZ. Critical revision: FNKK, ZZ, JM. Project Administration: FNKK. All authors read and approved the final manuscript.

Declaration of Competing Interest

None.

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Part of the material in the manuscript was presented orally at the 11th Pan-Pacific Conference on Rehabilitation (PPCR) on 17th-18th November 2018 in Hong Kong.

Five	<ol style="list-style-type: none"> Shoulder, elbow, and wrist coordinated movement Coordinating mild grasp and release in shoulder, elbow, and wrist control training 	<ul style="list-style-type: none"> - Grasping a bottle and putting it on the box ahead with shoulder flexion and elbow extension - Wrist movement in all directions - Turning over a block with forearm supination and pronation - Grasping three blocks in hand and release - Finger opposition to index and middle fingers
Six	<ol style="list-style-type: none"> Fine motor skills training Individual finger movement Grasp and release training Endurance training 	<ul style="list-style-type: none"> - Finger opposition to ring and little fingers - Reaching out and clipping clothes pegs - Small ball shifting in hand - Coin shifting using radial three fingers
Seven	<ol style="list-style-type: none"> Finger motor skills training Endurance, speed, and coordination in arm use 	<ul style="list-style-type: none"> - Finger opposition in a fast manner - Pen shifting using fingers - Card translation between fingers

^a FTHUE = Functional Test for the Hemiplegic Upper Extremity.

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