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The Effects of Unihemispheric Concurrent Dual-Site Transcranial Direct Current Stimulation on Motor Sequence Learning in Healthy Individuals: A Randomized Clinical Trial

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Abstract

Background: Unihemispheric concurrent dual-site anodal transcranial direct current stimulation (a-tDCS$_{UHCDS}$) of the primary motor cortex (M1) and dorsolateral prefrontal cortex (DLPFC) are introduced as effective techniques on M1 corticospinal excitability enhancement and its after-effects.
Objectives: The current study aimed at investigating the potential effects of multiple sessions of a-tDCS$_{UHCDS}$ of M1-DLPFC on motor skills learning in healthy individuals.
Methods: The randomized, clinical trial was conducted on a total of 37 volunteers completed all sessions of the study and were randomly divided into two groups of a-tDCS$_{UHCDS}$ and sham stimulation by the block randomization method. The current study was performed from January to May 2017 in Iran. Participants attended daily 20-minute motor training sessions for three consecutive days, while they concurrently received a-tDCS. Motor skills were assessed before the intervention (day 1), immediately after the intervention (day 3), and one week after the completion of the intervention.
Results: A total of 37 participants were included in the data analysis. Immediately after the completion of the intervention on day 3, mean skills in the experimental and control groups were 0.33 and 0.30, respectively. One week after the completion of the intervention, mean skills in the experimental and control groups were 0.36 and 0.29, respectively. The trend of motor learning considerably increased in the experimental (0.17; $P < 0.001$) and control (0.11; $P < 0.001$) groups. No significant difference was observed in motor learning immediately after the intervention between the groups ($P = 0.23$), while there was a significant difference in long-term offline learning between the groups ($P = 0.04$).
Conclusions: Greater motor skills in the a-tDCS$_{UHCDS}$ group compared with the sham tDCS group at one-week retention indicated the robustness of the a-tDCS$_{UHCDS}$ effect.

Keywords: Learning, Motor Cortex, Motor Skills, Prefrontal Cortex, Transcranial Direct Current Stimulation

1. Background

Learning motor skill is an important issue in individuals' lives or during the rehabilitation of patients with neurological disorders (1-3). Effects of repeated practice resulting in learning gains could happen within one or multiple sessions of online or offline learning (4, 5). Online or offline learning gains can be maintained over time, leading to long-term retention (6). The process of motor learning leads to triggering neuroplastic changes within different brain areas (1, 7). One of the brain areas involved in motor learning is the primary motor cortex (M1) (4).

Due to motor cortex plasticity during motor learning, non-invasive brain stimulation techniques such as transcranial direct current stimulation (tDCS) hold promise to improve motor learning through changes in corticospinal excitability (CSE) (8, 9).

The previous studies revealed that applying one session of anodal-tDCS (a-tDCS) over M1 can effectively enhance motor learning (10, 11). Also, recent studies showed that the simultaneous application of multiple sessions of conventional M1 a-tDCS and motor training lead to prolonged and larger after-effects (5, 12, 13). This is potentially

interesting, considering that despite the attention paid to a-tDCS of M1 as a potential tool to enhance motor learning, only a small number of multiple session motor learning studies are conducted (5, 12, 13). Vaseghi et al. revealed that unihemispheric concurrent dual-site a-tDCS (a-tDCS$_{UHCDS}$) of the M1-dorsolateral prefrontal cortex (DLPFC) considerably increased M1 CSE twice more than that of conventional a-tDCS M1, and lasted over 24 hours. This indicated the beneficial effects of a-tDCS$_{UHCDS}$ of M-DLPFC on the size and lasting of M1 CSE (14).

Due to the fact that M1 has an important role in the offline stabilization of motor learning, it appears that the simultaneous application of multiple sessions of a-tDCS$_{UHCDS}$ of M-DLPFC and motor tasks can profoundly enhance the size and lasting of the motor skill learning. To the best of authors' knowledge, no study investigated the effects of multiple sessions of a-tDCS$_{UHCDS}$ of M1-DLPFC on the motor sequence learning. The strength of the current study was to determine more effective a-tDCS interventions to induce prolonged and larger after-effects. Therefore, the novelty of the study was to introduce a-tDC$_{SUHCDS}$ approach to the size and lasting of the induced enhancement of motor skill learning.

2. Objectives

The current study aimed at investigating the potential effects of multiple sessions of a-tDCS$_{UHCDS}$ of M1-DLPFC on the size and lasting of the motor sequence learning in healthy individuals.

3. Methods

3.1. Study Design, Participants, and Setting

A randomized, clinical trial with a single-blind, parallel-group, and sham-controlled study design was used in which university students were recruited from governmental rehabilitation centers through advertisement. The current study was performed from January to May 2017 in the rehabilitation research center, department of Physiotherapy, University of social welfare and rehabilitation Sciences, Tehran, Iran. The study protocols were approved by the human ethics committee at the University of Social welfare and Rehabilitation Sciences, Tehran, Iran (IR.USWR.REC.1394.222). The current study was also registered in the Iranian registry of clinical trials (registration number: IRCT2016071028808N2, www.irct.ir).

The healthy university students included males and females, ranging from 19 to 35 years enrolled to participate in the current study based on a simple non-probability sampling method.

The inclusion criteria were no previous neurological or psychiatric conditions, no visual or auditory conditions, no musculoskeletal disorders especially in the upper extremity, and no perceptual or memory problems (mini-mental state examination (MMSE) > 23 out of 30). The exclusion criteria were any contraindications to application of tDCS such as skin abnormalities (cut, abrasion, rash) in the stimulation area, any intracranial metal implantation, pacemaker, any other heart condition or epilepsy. All participants required a general physical and neurological examination and signed the informed consent forms before participating in the study. The current study met the criteria in a CONSORT checklist.

To calculate the sample size, according to the pilot study on nine participants, considering the mean and standard deviation (SD) of outcome measure in each group ($mean_1$ = 0.42, SD_1 = 0.2) ($mean_2$ = 0.21, SD_2 = 0.07), type 1 error (α = 0.05) and type 2 error (β = 0.02), the number of individuals required per group was 16. Also, eight other individuals were added to the sample size, given an anticipated dropout rate of 25%. Thus, a sample size of twenty individuals per group was necessary.

$$N = \frac{\left(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta}\right)\left(\sigma_1^2 + \sigma_2^2\right)}{\left(\mu_1 - \mu_2\right)^2} \quad (1)$$

3.2. Randomization and Interventions

Block randomization method was conducted by a computer-generated random number list designed to randomize subjects into experimental and sham-control groups by an independent researcher and the allocation ratio was 1:1 using random block sizes of two.

Groups of participants received a-tDCS under each of the two different experimental conditions in a random order: 1, serial response time test (SRTT) training + a-tDCS$_{UHCDS}$ of M1-DLPFC; 2, SRTT training + sham a-tDCS$_{UHCDS}$ of M1-DLPFC. Training programs were performed by the same observer (first author). Treatment consisted of twenty minutes of SRTT training sessions over three consecutive days, while concurrently tDCS was applied at the same time (mornings or early afternoons) each day (day 1, day 2, and day 3). The same instruction was provided to the participants by the researcher who applied the stimulation (first author). Participants were blinded to the active and sham conditions of a-tDCS; it means that the participants were completely unaware of the type of stimulation (active or sham).

3.2.1. Serial Response Time Task

Participants were seated in front of a computer screen at eye level behind a response pad with four buttons numbered 1 to 4. A visual cue (small black circle) appeared

in one of the four positions horizontally spaced from left to right on a white screen background. Participants were instructed to respond to visual cues by pressing the corresponding button with the corresponding finger of the right hand. When the correct key was pressed, the target visual cue disappeared. Afterward, with a short fixed delay (500 ms), the next stimulus came on fourth and the blocks of visual cues were presented unpredictably (10, 15). The main training task consisted of eight blocks of 120 keypress stimuli over three consecutive days. Presentation of circles was repeated sequence in all blocks except in blocks 1 and 6, which the circles were presented in random. In Blocks 2 to 5 and 7 and 8, the same 12-trial sequence of circle positions repeated itself ten times (142134213243). Also, two sequenced blocks were used as a baseline assessment (before intervention) on day 1, immediately post-intervention on day 3, and one week after the last intervention session.

3.2.2. Transcranial Direct Current Stimulation

A-tDCS was applied via two saline-soaked surface sponge electrodes delivered from a battery-driven, constant current stimulator (ActivaDose®II; Iontophoresis Delivery Unit, USA). For a-tDCS$_{UHCDS}$ and sham a-tDCS groups, two separate active anode electrodes (2 × 3 cm) were placed over F3, and C3 (international 10 - 20 system) corresponding left DLPFC and M1, respectively. Two separated return electrodes (2 × 6 cm) were also placed over the contralateral supraorbital area (14, 16, 17). Therefore, two single channel stimulator devices were used in all individuals. In the experimental group, both devices connected to the active electrodes over M1 and DLPFC were turned on. In the sham-control group, both devices were turned on for only 1 minute. The tDCS stimulators were set to deliver 1 mA direct current (DC) for 20 minutes, with 10 seconds of linear fade in and fade out to minimize the side effects (8, 18).

3.3. Outcome Measures

Skill can be defined as the improved trade-off between speed and accuracy (12, 19). The speed was defined as the change in the response time during sequential trials (15). Accuracy was defined as the percentage change in the total number of correct responses. The mean response time and accuracy were measured for each block of 120 key-press stimuli. Improvement in skill during the SRTT task provides the evidence of the occurrence of motor skill learning (12, 19). In the current study, any change in the acquired skill, which happened immediately after the completion of the intervention on day 3 (post-intervention time point) was considered as the outcome measurement to assess motor skill learning immediately post-intervention. Also, any change in the skills occurring up to one week after the three sessions (retention time point) was considered long-term offline learning.

3.3.1. Skills

The skill index (SI) was calculated by dividing the percentage of correct sequences by the mean time of responses per block, which provided both the speed and accuracy requirements (12, 19).

3.3.2. Assessment of the Side Effects

A questionnaire using numerical analog scales (NAS) was used to assess the adverse effects during tDCS sessions (18). NAS ranges 0 to 10; 0 is rated as no sensation and 10 rated as the worst sensation imaginable.

3.4. Statistical Analyses

Statistical analyses were performed based on 'per protocol' approach. To test normality, that is, to check if the distribution of data was parametric, the Kolmogorov-Smirnov (K-S) test was employed. A two-way repeated measure ANOVA was used to evaluate the effects of groups and time points and their interaction with motor skills learning. Additionally, to test whether the baseline value of each group differed significantly from time points, a paired-sample t-test using the least significant difference (LSD) adjustment was used. Also, intergroup differences were assessed with the independent t-test. All analyses were performed with SPSS version 22.0 (IBM Corp., Armonk, N.Y., USA) P value > 0.05 was considered statistically significant.

4. Results

At first, 44 volunteers were assessed for eligibility, and after the screening, 41 were enrolled in the study; three participants did not meet the inclusion criteria. As indicated in Figure 1, four participants did not complete all the three sessions of the study due to personal problems. Therefore, only data from 37 participants were included in the statistical analysis, and there were no missing data (Figure 1).

The training data were normally distributed as evaluated by K-S test (P > 0.05). Demographic details and baseline data of the participants in the two groups are presented in Table 1. At baseline, no significant differences were observed in terms of gender, age, MMSE, and baseline skill scores between the groups (P > 0.05).

4.1. The Effects of a-tDCSUHCDS on Skills

Results of a mixed-model and repeated measure ANOVA are presented in Table 2. The interaction between time and group was significant (P = 0.03), which indicated differences in the trend of learning between the

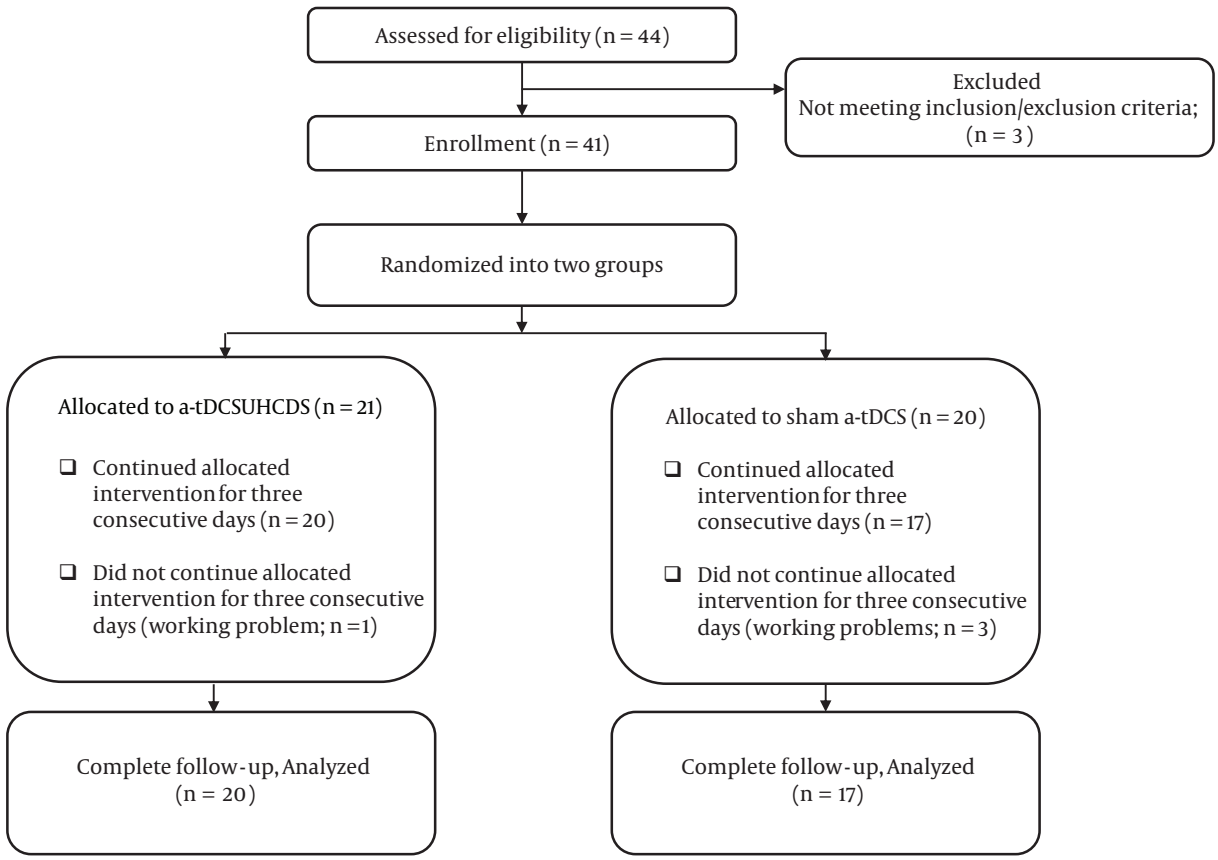

Figure 1. Flow diagram of study participants: Eligibility assessment, enrollment, group allocation, and analysis

Table 1. The Baseline Characteristics of the Study Participants[a]

Variable	Exp (N = 20)	Con (N = 17)	P Value
Gender (male/female)	6/14	4/13	0.85
Age, y	27.90 ± 0.87	27.83 ±0.83	0.84
MMSE test	29.70 ± 0.12	29.61 ± 0.18	0.89
Skill	0.19 ± 0.01	0.19 ± 0.008	0.81

Abbreviations: Con, Control Group; Exp, Experimental Group; SEM, Standard Error of Measurement; MMSE, Mini-Mental Status Scale.
[a]Data are expressed as mean ± SEM.

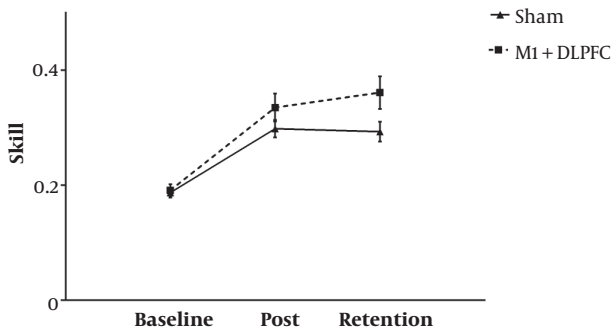

Figure 2. The Trend in the mean and SEM of skills for M1 + DLPFC (black squares) and sham (black triangles) a-tDCS groups

groups at different time points. The trend of motor skill learning increased in the experimental (0.17; $P < 0.001$) and control (0.11; $P < 0.001$) groups (Figure 2). The mean skill of different time points for both groups is presented in Table 3. The results of independent t-test revealed no significant difference in motor learning immediately after intervention between the groups ($P = 0.23$), while there was a significant difference in long-term offline learning between the groups ($P = 0.04$) (Figure 3).

4.2. Safety and Side Effects

All individuals rated their sensations under the electrodes over three consecutive sessions (Table 4). Most participants reported sensations under the electrodes were itching and tingling in all experimental sessions. No ad-

Table 2. The results of a Mixed-Model and Repeated Measure ANOVA

Outcome Measure	Main and Interaction Effects	Df	F	P Value
Skills	Time (intragroup effects)	2	84.96	< 0.001
	Time * group (interaction effects)	1.81	3.75	0.03
	Group (intergroup effects)	1	2.28	0.14

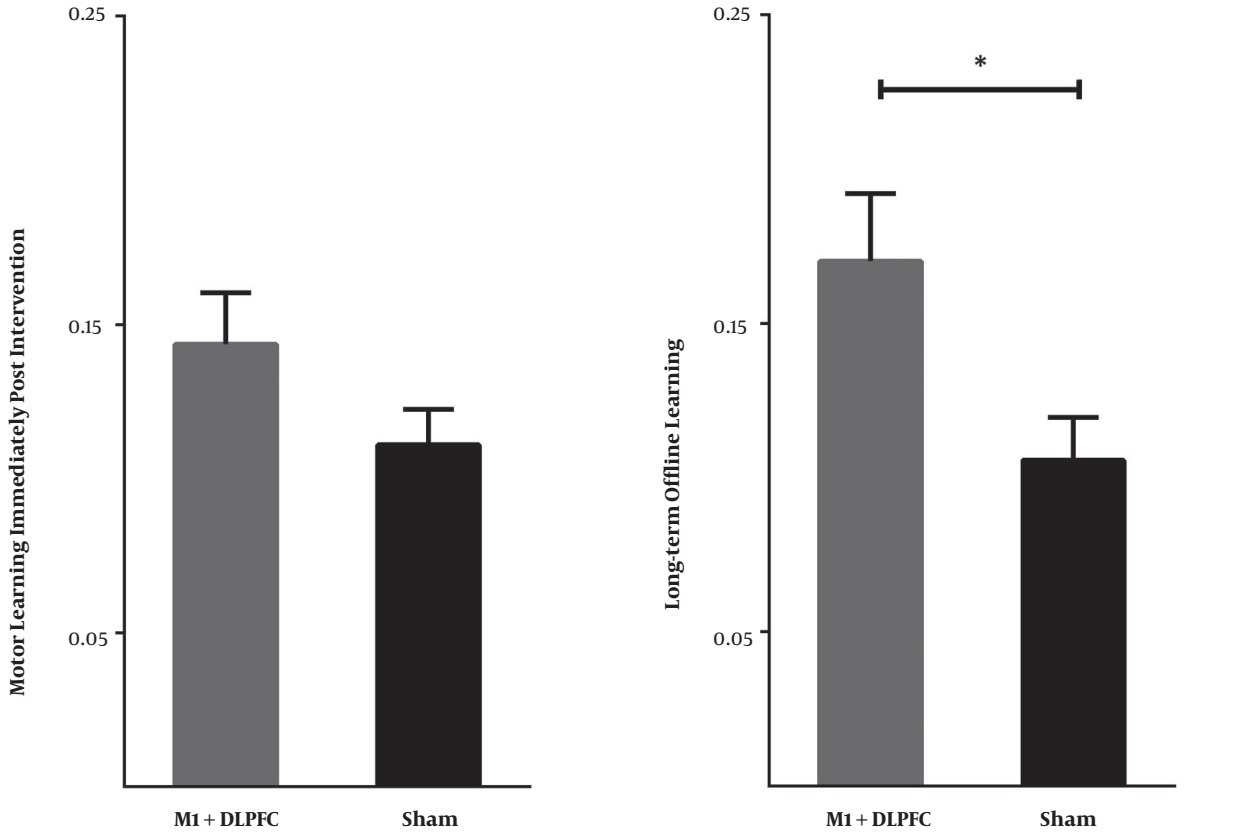

Figure 3. Changes in skills between baseline and post-intervention (motor learning immediately post intervention), as well as baseline and retention (long-term offline learning) (mean differences ± SEM)

Table 3. Intervention Outcomes[a]

Skill	Group		P Value
	Sham a-tDCS	A-tDCS$_{UHCDS}$ of M1 + DLPFC	
Baseline	0.19 ± 0.008	0.19 ± 0.01	0.77
Post-intervention	0.30 ± 0.02	0.33 ± 0.02	0.23
Retention	0.29 ± 0.02	0.36 ± 0.03	0.04

[a] Data are expressed as mean ± SEM.

verse effects such as headache or pain were reported during or after stimulation.

5. Discussion

The results of the current study indicated a significant difference in long-term offline learning between the a-tDCS$_{UHCDS}$ and sham tDCS groups. The results also revealed that motor learning remarkably improved immediately after multiple sessions of simultaneous a-tDCS and motor training.

It appears that a-tDCS applied during three consecutive daily sessions of motor training was associated with a cumulative motor skill improvement.

The current research also indicated that the application of multiple sessions of a-tDCS$_{UHCDS}$ of M1-DLPFC led to a positive trend toward long-term offline learning effects.

Table 4. Numeric Sensation Scores Under the Electrodes During Stimulation Sessions[a]

Side Effects	A-tDCS$_{UHCDS}$ of M1 + DLPFC			Sham a-tDCS		
	Day 1	Day 2	Day 3	Day 1	Day 2	Day 3
Tingling	4.95 ± 0.14	4.90 ± 0.20	4.75 ± 0.21	2.44 ± 0.12	2.38 ± 0.11	2.22 ± 0.10
Itching	2.85 ± 0.33	2.75 ± 0.33	2.75 ± 0.32	1.38 ± 0.29	1.50 ± 0.29	1.61 ± 0.31
Burning	0.47 ± 0.28	0.85 ± 0.36	0.95 ± 0.38	-	-	-
Not tolerated	-	-	-	-	-	-

[a] Scores are reported as mean ± SEM.

The current study findings were in line with those of previous findings indicating beneficial effects of multiple sessions of a-tDCS on learning tasks (5, 12, 13).

Findings of the current study also indicated no significant difference in skills between a-tDCS$_{UHCDS}$ and sham groups immediately postintervention. These findings were in line with those of the previous studies reporting that motor learning following application of a-tDCS over M1 was not significantly different from sham a-stDCS immediately after training in healthy individuals (19-21). In contrast, Nitsche et al. found that compared with sham tDCS, a-tDCS of M1 induces a significant improvement of motor performance. The reason for this discrepancy may lie on the methodological differences between the two studies. Nitsche et al. used a protocol calculating the response time (10), while the current study findings were obtained using a compound measurement calculating motor performance as a function of both the response time and accuracy.

Also, the findings of the current study revealed that a-tDCS$_{UHCDS}$ induced more long-term offline learning effect compared with sham tDCS. These findings were in line with the findings of the previous studies indicating beneficial lasting effects of M1 a-tDCS during motor learning (5, 12). These findings supported the idea that M1 was a key structure in the offline stabilization of motor learning (5, 12). Reis et al. revealed positive effects of M1 a-tDCS on learning up to three months after the completion of multiple sessions of sequential visual isometric pinch task (SVIPT). Marquez et al. also indicated positive effects of M1 a-tDCS on long-term retention (up to one week) during multiple sessions of SVIPT, while the current study indicated the lasting effects of a-tDCS$_{UHCDS}$ of M1 -DLPFC on learning up to one week after the completion of multiple sessions of SRTT.

On the other hand, some single-session studies revealed positive lasting effects of M1 a-tDCS on learning task only up to 24 hours (11, 22). The reason behind the longer lasting effect in the current study compared with these studies (11, 22) lies in the multiple session nature of the current study. Also, most of the previous studies applied conventional M1 a-tDCS electrode montage during a motor training task (10-13), while the current study applied an alternative electrode montage during SRTT.

Findings of the current study supported the hypothesis that a-tDCS$_{UHCDS}$ plays an essential role in obtaining the desired result.

It is noted that the advantage of this new approach is more likely to be site-specific caused due to the coactivation and functional connectivity between M1 and DLPFC (14, 23).

The strong point of the current study was using small size of active electrodes producing highly focused effects over the target areas (14, 16, 17, 24).

Therefore, it might be speculated that multiple sessions of a-tDCS$_{UHCDS}$ during a motor training task considerably increases the firing rate of neurons and raises the strengthening of learning-related synaptic connections; thereby resulting in long-term offline learning (25).

Given the increasing interest in the clinical utility of a-tDCS as an adjuvant strategy to physical therapy, the beneficial long-lasting effects of a-tDCS$_{UHCDS}$ should be explored further in future studies.

5.1. Limitations

The current study had some weak points. Most of the participants were female students. The effects of gender differences in responses to a-tDCS$_{UHCDS}$ were not determined. The current study assessed motor learning in young healthy individuals. Therefore, the results cannot be generalized to patients or older people. Also, the differential effects of a-tDCS$_{UHCDS}$ and conventional M1 a-tDCS on the size and lasting of the induced enhancement of motor learning were not determined in the healthy individuals. Therefore, future studies are needed to clarify the findings.

5.2. Conclusion

The current study revealed a significant increase in long-term offline learning by a-tDCS$_{UHCDS}$ technique. This provided evidence for the priming effects of a-tDCS$_{UHCDS}$ on skill acquisition in a healthy individual and possibly patients with neurological conditions.

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