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Transcranial direct current stimulation over the motor and premotor cortex with mirror therapy improves motor control, muscle function, and brain activity in chronic stroke: a double-blind randomized sham-controlled trial

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Abstract

Background Transcranial direct current stimulation (tDCS) is a popular approach to augment the effects of neurorehabilitation. Most studies stimulated the ipsilesional primary motor cortex (iM1); nonetheless, the success of iM1 stimulation was variable, suggesting that it may not be optimal for improving recovery. Ipsilesional premotor cortex (iPMC) may be an alternative candidate based on its likelihood of survival post-stroke and its contribution to functions. This study aimed to determine the effects of tDCS on the iPMC and iM1 with mirror therapy (MT) on motor control, muscle function, and brain activity in chronic stroke.

Methods Thirty-six participants were randomly distributed into (1) iPMC-tDCS with MT (PMC) (2), iM1-tDCS with MT (M1), and (3) sham tDCS with MT (sham). Motor control was assessed using kinematics. Muscle function was assessed using the modified Ashworth and the Medical Research Council Scales. The M1 and PMC activity was recorded using electroencephalography (EEG), and the event-related desynchronization and the laterality index (LI) were examined.

Results Significant within-group differences were identified in the kinematic outcomes. After interventions, the PMC group showed reduced paretic upper limb muscle spasticity and improved paretic limb control with greater movement smoothness and peak velocity. The M1 group showed reduced trunk compensation with fewer trunk displacement and flexion. However, the sham group relied more on trunk compensation, demonstrating increased trunk peak velocity and smoothness. Significant between-group differences were also found in paretic limb control and trunk displacement. Post-hoc analysis revealed that the PMC group improved paretic limb control, and the M1 group showed reduced trunk displacement more than the sham group. Significant within-and between-group differences were identified in EEG outcomes. The iM1 and contralesional PMC (cPMC) activity increased from pre-

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to-post intervention in the M1 group. In contrast, the iM1 activity decreased, and the LI declined from pre- to post-intervention in the sham group. Significant group differences were found in the iM1 activity, with the PMC and M1 having greater iM1 activation than the sham group.

Conclusions Differential treatment benefits were identified between iPMC- and iM1-tDCS with MT. iPMC-tDCS with MT uniquely improved paretic upper limb control with reduced muscle spasticity while iM1-tDCS with MT mitigated trunk compensation during reaching. These findings suggest that both iPMC- and iM1-tDCS could augment the effects of stroke neurorehabilitation and may be considered in clinical applications.

Trial registration ClinicalTrials.gov Identifier: NCT04655209. Registered on 15th November 2020. https://clinicaltrials.gov/study/NCT04655209.

Keywords Transcranial direct current stimulation, Mirror therapy, Rehabilitation, Kinematics, Reach, Stroke, Motor control, Event-related desynchronization, Electroencephalogram

Introduction

Stroke remains one of the leading cerebrovascular diseases causing long-term disability [1]. Individuals often suffer from upper extremity hemiparesis after a stroke, which impairs their ability to perform daily activities and reduces their quality of life [2, 3]. There is an urgent need to identify rehabilitation approaches to enhance upper extremity recovery and improve daily function in stroke patients.

Various neurorehabilitation approaches have been developed to enhance stroke recovery [4]. One promising approach is mirror therapy (MT). MT is a repetitive, task-oriented approach that utilizes mirror visual feedback (MVF) to augment motor re-learning [5]. During MT, a mirror or mirror box is placed in the stroke participants' midsagittal plane. The paretic arm is placed inside the mirror box and the non-paretic arm is in front of a mirror, outside the box. Participants are instructed to look at the mirror reflection of the non-paretic arm and imagine it is the paretic arm while practicing bilateral movements as simultaneously as possible. The MVF during MT gives participants the illusion that their paretic arms move the same as the non-paretic arm, and together with the real-time practice of the paretic arm, it could help restore the efferent-afferent loop that was impaired after stroke and facilitate recovery [5–7]. A recent Cochrane review has shown a reduction of motor impairment and functional improvements after MT in chronic stroke patients [8].

In addition to MT, brain neurotechnology has emerged as a promising approach to facilitate neuronal recovery in stroke patients. Brain neurotechnology uses equipment/techniques to increase/decrease brain excitability and seeks to accelerate neuronal recovery in the brain [9]. Transcranial direct current stimulation (tDCS) is a popular brain neurotechnology, which modulates cortical excitability through a weak direct current. This weak direct current can change the membrane potential of neurons and lead to neuronal depolarization or hyperpolarization, which in turn increases/decreases brain excitability and facilitates neuronal recovery [10–12]. Current evidence suggests that applying brain neurotechnology, such as tDCS before rehabilitation therapies could generate greater treatment effects than rehabilitation therapies alone [13, 14]. Hence, tDCS has become a popular approach to prime neurorehabilitation to augment treatment benefits in stroke patients.

To our knowledge, three randomized controlled studies have combined tDCS with MT [15–17]. Cho et al. (2015) applied tDCS before MT or motor training without MVF and found significant improvements in the paretic hand strength and dexterity in the tDCS with MT than the non-MVF training group. The other two studies applied tDCS sequentially or concurrently with MT to investigate the timing effects of tDCS. One study found concurrent application of tDCS with MT improved hand function [15]. In contrast, the other study found sequential application of tDCS before MT enhanced ADL/instrumental ADL (IADL) function and finger motor control [17]. Despite the heterogenous findings of tDCS timing effects, the above suggests that applying tDCS with MT has the potential to augment paretic arm/hand recovery of stroke patients than applying tDCS with non-MVF motor training; Furthermore, these heterogeneous findings between studies also indicate that there may be factors, other than the timing effect, need to be considered when uses tDCS to prime MT [18, 19].

One such factor could be the cortical region of stimulation. Most studies have applied anodal tDCS on the ipsilesional primary motor cortex (iM1) intending to facilitate paretic arm/hand recovery [13]. Nevertheless, some neurons in the iM1 may have been impaired due to stroke, and stimulation of iM1 could activate the remaining intact iM1 neurons only, which may not always be effective for facilitating neuronal or functional recovery [20–22]. Another potential candidate for cortical stimulation is the ipsilesional premotor cortex (iPMC). Compared to the iM1, neurons in the iPMC may have greater chances of surviving after a stroke [23, 24]. Studies have found an increased activation of iPMC during motor tasks and that disruption of iPMC significantly affected

paretic arm/hand motor control [25–28]. A recent study also demonstrated anodal tDCS on iPMC with rehabilitation training improved motor function in stroke patients [29]. The above findings of iPMC associated with stroke motor recovery suggested that iPMC may be an alternative candidate to iM1 to augment the treatment effects of MT. To date, no studies have compared the effects of anodal tDCS on iM1 vs. iPMC with MT in individuals with chronic hemiparesis. Which one of them may be a better brain stimulation target to augment the effect of neurorehabilitation therapies remains largely unexplored.

Another crucial factor to consider when investigating the augmentative effects of brain stimulation on neurorehabilitation is the treatment outcomes. Most tDCS studies included only clinical outcome measures to assess motor recovery; however, these clinical measures may not be sufficiently sensitive to capture changes in movement performance and motor control strategies [30, 31]. Kinematic assessment has been recommended as a sensitive and valid method to capture movement performance and motor control changes in stroke patients [32]. It can measure spatial and temporal characteristics of movements and uncover the motor control strategy (e.g., end-point control and trunk contributions) stroke patients used during functional tasks. Furthermore, kinematic parameters such as peak velocity, movement units, and joint movement angle can provide detailed information on whether a true behavioral recovery or compensation has occurred after interventions and unravel the true treatment benefits of neurorehabilitation [32, 33]. To our knowledge, only one previous study that combined iM1-tDCS with MT evaluated movement kinematics in chronic stroke patients [17]. No studies have examined and compared the effects of iPMC- vs. iM1-tDCS with MT on movement performance and motor control strategies using kinematic assessments in chronic stroke patients.

In addition to kinematic outcomes, assessing changes in cortical activity using neurophysiological measurements such as electroencephalography (EEG) is crucial for unraveling the modulatory effects of brain stimulation in stroke patients. Specifically, event-related desynchronization (ERD), the decrease in the EEG power band, could be a reliable outcome to indicate changes in cortical activity [34]. Studies have found that an increase of ERD in the mu rhythm (i.e., 8–12 Hz) correlates with increased cortical excitability or activated cortical region and is associated with mirror visual feedback and tDCS [35–38]. Therefore, mu ERD could be an appropriate and effective index for neuronal recovery in the brain and may help to differentiate the modulatory effects between iPMC- and iM1-tDCS [39].

This study aimed to determine the effects of anodal tDCS on iPMC and iM1 compared to sham stimulation with MT in individuals with chronic hemiparesis. In particular, we examined motor control using kinematic assessments and evaluated muscle function (i.e., muscle spasticity and muscle strength). We also assessed brain activity (i.e., the mu ERD) using EEG to determine the modulatory effects of iPMC- and iM1-tDCS on the lesioned and non-lesioned hemispheres. We hypothesized that there might be differential treatment effects on motor control, muscle function, and brain activity between iPMC-, iM1-, and sham tDCS with MT in the participants.

Methods

Participants

Individuals were recruited from hospitals in Taiwan. The inclusion criteria were [1] a first-ever, unilateral stroke [2], stroke onset ≥ 6 months [3], age between 45 and 85 years old, [4] the Fugl-Meyer assessment of upper extremity (FMA-UE) scores between 18 and 56, indicating mild to moderate impairment [40], (5) able to follow instruction (i.e., the Mini-Mental State Examination (MMSE) scores ≥ 24) and [6] no excessive muscle spasticity (i.e., the Modified Ashworth Scale scores < 3) of all joints in the paretic upper limb. The exclusion criteria were [1] participation in other rehabilitation studies or drug experiments [2], concomitant neurologic, neuromuscular, or orthopedic conditions such as brain tumor, cerebral edema, or Parkinson's disease [3], unstable cardiovascular status such as uncontrolled hypertension or New York Heart Association (NYHA) Class III/IV heart failure [4], had Botulinum toxin injections in the paretic upper limb in the past 3 months [5], severe vision or visual perception impairments (e.g., neglect and poor visual field) as assessed by the National Institutes of Health Stroke Subscale, and [6] any contradictions to non-invasive brain stimulation (NIBS), skin lesions on the electrode sites, or being not suitable for using tDCS by the physician's assessment [41]. All participants gave the written informed consent before enrollment into this study. This study was approved by the Institutional Review Board of Chang Gung Memorial Hospital, Taoyuan, Taiwan. All study procedures were conducted strictly following the Declaration of Helsinki.

Design

This study was a double-blinded, randomized controlled trial with pre-intervention and post-intervention assessments (Fig. 1). Participants were stratified based on their baseline upper extremity motor impairment (i.e., FMA-UE scores, 18–39 vs. 40–56) and the lesioned side of hemispheres (right vs. left) and randomly assigned to one of the following three groups: [1] iPMC-tDCS with MT (i.e., the PMC group) [2], iM1-tDCS with MT (i.e., the M1 group), and [3] Sham stimulation with MT (i.e., the

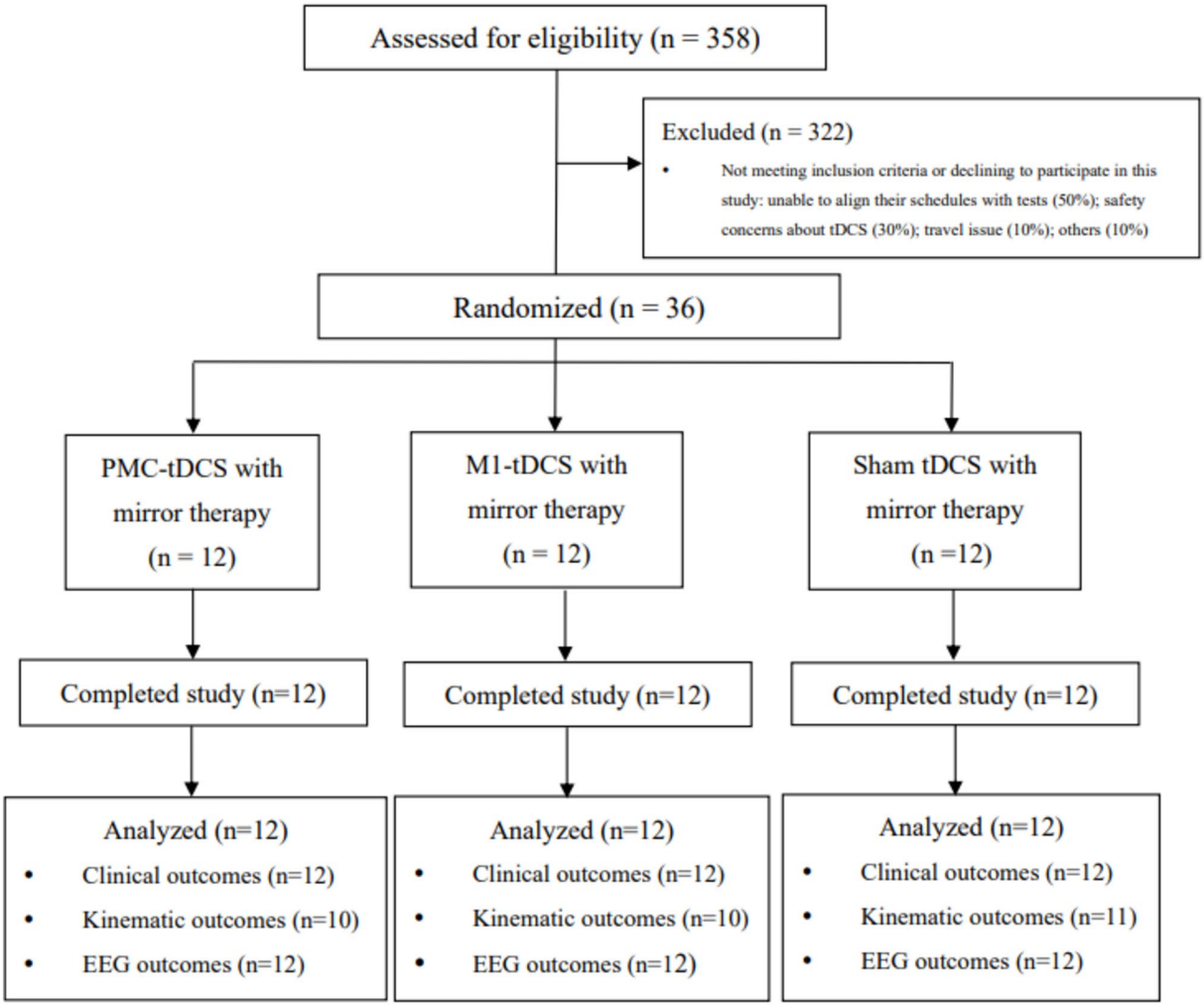

Fig. 1 The CONSORT flow diagram

sham group). Randomization was performed using a randomization table provided at http://www.randomizer.org/ (free available online).

Participants were assessed one week before and after intervention by a rater (an occupational therapist) blinded to the purpose of this study and the participant's group assignment. This rater was trained by senior occupational therapists and the principal investigator of this study to ensure he/she performed assessments in the correct and standardized way. This rater was not involved in any intervention of this study. Clinical assessments were performed at the hospital and the neurophysiological (i.e., EEG) and kinematic assessments were implemented in the research laboratory within one week before and after interventions. Rest breaks were provided during assessments to minimize fatigue.

Intervention protocols

Participants received one of the three interventions: [1] iPMC-tDCS with MT (i.e., the PMC group) [2], iM1-tDCS with MT (i.e., the M1 group), and [3] sham stimulation with MT (i.e., the sham group) for 90 min/day, 3–5 days/week with a total of 20 sessions. tDCS and MT were provided in a sequential order. In each training session, participants underwent 20 min of active or sham stimulation, and after the stimulation was completed, they practiced 40 min of MT and 30 min of functional task practice (Fig. 2).

tDCS protocols

A battery-driven direct current stimulator (StarStim, Neuroelectrics, Barcelona, Spain) was used to deliver tDCS. The anode electrode was placed on iPMC or iM1, which was the F3/F4 or C3/C4 location of the international 10–20 EEG electrode system, depending on the

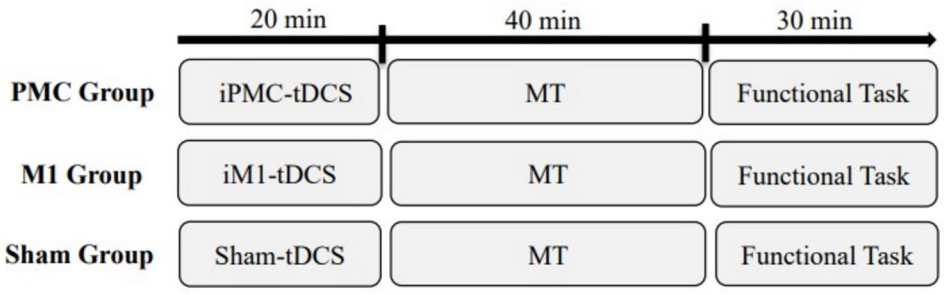

Fig. 2 The experimental flow of the three groups. Note: PMC, iPMC-tDCS with MT group; M1, iM1-tDCS with MT group; Sham, Sham-tDCS with MT group; MT, mirror therapy; tDCS, transcranial direct current stimulation; min, minutes

group the participant was allocated to. The F3/F4 were selected for iPMC stimulation because these electrodes were on the area commonly defined as PMC in brain stimulation studies [42–44].

The duration of anodal tDCS was 20 min and the intensity was 2 mA. The electrode size was 3.14 cm^2 resulting in a density of 0.06 A/m^2, which was well within the safety limit [45]. The cathode electrode was placed at the contralesional supraorbital cortex (i.e., Fp1/Fp2 location of the international 10–20 EEG electrode system). For the sham stimulation, the current was first ramped up to 2 mA in 15 s and then ramped down to 0 in the next 15 s to provide a sensation similar to that of active tDCS. To ensure blindness, the same tDCS device, including the cap and electrodes, was used for real and sham stimulation. In addition, participants were naïve to brain stimulation before participating in this study.

MT and functional task practice

A mirror box (size: 48.5*34*35 cm) was placed on a table in the participants' mid-sagittal plane during MT. Participants were seated with their paretic arms in the mirror box and their non-paretic arms in front of the mirror. Participants were instructed to look at the mirror reflection of the non-paretic arm, imagine it was the paretic arm, and perform bilateral movements as simultaneously as possible. The MT protocol consisted of two types of movements: [1] the intransitive movement involving proximal and distal arm/hand movement practice, such as elbow flexion/extension, forearm pronation/supination, and wrist flexion and extension, and [2] the transitive movement involving object manipulation, such as flipping a card, placing marbles in a bowl or placing pegs in a board [46]. The functional task training focused on the practice of everyday activities that were essential and meaningful for the participants. The therapists discussed with participants the daily tasks that he/she considered meaningful and designed functional task training according to the participant's needs. Examples of functional task practice included stabilizing a bowl using the non-paretic hand and scooping food out of the bowl using the paretic hand, grasping a cup of water with the paretic hand, and bringing it to the mouth, or folding towels/clothes using both hands. Common daily objects, such as towels, bowls, and bottles were used for functional task practice based on the demand of the task. Participants performed MT for 40 min followed by functional task practice for 30 min [17, 46].

Outcome measures

Primary outcome: kinematics

A unilateral reach-to-target task was used to evaluate paretic upper limb and trunk movement kinematics. Participants were seated in front of a table with the seat height adjusted to participants' lower leg length. Participants placed their paretic hands on the table at a marked starting point with their elbows maintained at approximately 90 degrees. They were asked to reach forward and press a doorbell positioned at 90% of their paretic upper limb length (from the acromion to the third fingertip) along the midsagittal plane as quickly as possible when they heard a bell ring. If the participants' maximal reaching distance was less than 90% of the paretic upper limb length, the reaching distance was adjusted to their maximal reaching distance. There was one practice trial to ensure participants understood the task instructions and procedures. After the practice trial, participants performed the unilateral reach-to-target task three times. The kinematic data of these three trials were collected for analysis.

Movement kinematics were recorded using a seven-camera motion analysis system (VICON MX; Oxford Metrics Inc., Oxford, England). Thirteen reflexive markers were attached to the upper limb and trunk including the 7^{th} cervical vertebra (C7) and 4^{th} thoracic vertebra (T4) spinal processes, mid sternum, bilateral clavicular heads, and acromion, anterior aspect of the upper arm midway between the acromion and lateral epicondyle, lateral epicondyle, ulnar and radial styloid processes, and the tip of thumb and index fingers. The motion analysis system recorded marker positions in the three-dimensional space during the task at a sampling rate of 120 Hz

and digitally low-pass filtered at 5 Hz using a second-order Butterworth filter. Movement onset/offset was defined as the time when the tangential velocity of the paretic index finger rose above or below 5% of its peak value (i.e., peak velocity) [47]. A customized LabVIEW program (National Instruments Inc., Austin, TX) was used to process the kinematic data.

Kinematic variables included peak velocity (PV), movement time (MT), movement total displacement (TD), movement units (MU), and joint and trunk recruitments (i.e., maximal shoulder flexion and maximal trunk flexion). These kinematic variables were used to describe the movement performance of the paretic upper limb and trunk and can be categorized into two different motor control strategies: the paretic upper limb endpoint control strategy and the trunk compensation strategy [48]. The movements of the hand marker (the tip of the index finger) represented the endpoint control, and the movements of the sternal marker represented the trunk control [33, 48, 49]. PV was defined as the highest instantaneous tangential velocity of the marker during the task [50]. MT was defined as the time between movement onset and offset of the marker [50]. TD was defined as the path of the marker in the 3-dimensional space at x, y, and z coordinates from movement onset to offset [51]. A reduction in TD represented a shorter movement path. One acceleration and one deceleration phase comprised a MU and represented movement smoothness [52]. A decrement in the number of MU indicated smoother movements [52]. Maximal shoulder flexion was the maximal angle of shoulder flexion in the sagittal plane. The shoulder angle was defined as the angle between the vector joining the ipsilateral acromion-lateral epicondyle markers and the vector joining the C7–T4 markers [47]. Maximal trunk flexion was defined as the maximal angle of the trunk in the sagittal plane. The trunk angle was defined as the angle between the vector joining the C7-T4 markers at the trunk movement onset and offset [47]. Increment in maximal shoulder or trunk flexion indicated greater recruitments of the paretic upper limb or trunk during the reach-to-target task [32, 47, 48].

Secondary outcomes: clinical and EEG outcomes

Clinical outcomes: muscle function

The paretic upper limb muscle function including muscle spasticity and muscle strength was evaluated using the Modified Ashworth Scale (MAS) and the Medical Research Council Scale for Muscle Strength (MRC). The MAS uses a 5-point rating scale that assesses muscle spasticity of joints of the paretic upper extremity (i.e., the shoulder, elbow, forearm, wrist, and hand). The MAS scores of all joints were averaged to represent the overall muscle spasticity of the paretic upper limb. Higher scores indicate stronger muscle spasticity [53]. The MRC assesses muscle strength of the paretic upper limb with scores ranging from 0 (no visible contraction) to 5 (normal contraction). The muscle strength of shoulder flexors/abductors, elbow flexors/extensors, wrist flexors/extensors, and flexors/extensors of the metacarpophalangeal joints of the hands was graded and averaged across muscles to represent the overall muscle strength of paretic upper limb [54]. High scores indicate greater muscle strength. The psychometric properties of MAS and MRC have been established in stroke patients [53, 54].

EEG outcomes

Brain activity was recorded using an EEG system, the actiCAP system (Brain Products GmbH, Germany), with 32 electrodes placed on the scalp according to the international 10/20 system. The ground and reference electrodes were placed on FPz and TP10, respectively. Vertical and horizontal Electrooculography (EOG) were recorded using two pairs of electrodes: one above and below the eyes and the other lateral to the eyes. The impedance of all channels was kept below 25 kOhm throughout the assessment to ensure data quality. The EEG signal was amplified and digitalized (1000 Hz sampling frequency) using the actiCHamp equipment (Brain Products GmbH, Germany) and recorded using the BrainVision Recorder (Munich, Germany) synchronously during the experiment.

Participants were seated in front of a table with seat height adjusted to lower leg length and table height adjusted to 5 cm below the elbow. A computer screen was placed in front of the participant at eye level and a keyboard was placed on the table within participants' arm-reaching distance. Participants rested both forearms on the table with their shoulders relaxed and elbows maintained at approximately 90 degrees and in a stable sitting position. The EEG assessment session started with an 8-second period of a relaxed state, during which the word "Rest" was shown at the center of the screen. After "Rest," the word "Ready" was shown for 2 s to indicate the start of the assessment followed by the word "Start" with an arrow pointed to the left or right direction for 5 s [55, 56]. Participants were instructed to press the keyboard buttons as soon as they saw the arrows appear on the screen. They were required to press the keyboard button with their left or right hands corresponding to the side to which the arrow pointed [55, 56]. A total of two assessment sessions were conducted; each consisted of 100 trials (50 trials of the right arrow and 50 trials of the left arrow) with a total of 200 trials at the pre-and post-intervention, respectively. There was a 5-minute break provided between the two assessment sessions to minimize feelings of fatigue during assessments. The

participants practiced the required movement for four trials consisting of two left and two right arrows before the experiment started to ensure he/she understood the instructions and requirements.

Preprocessing of EEG data and quantification of event-related desynchronization (ERD)

The raw EEG data was filtered between 0.5 and 40 Hz with a 2nd order Butterworth filter and a 60 Hz-notch filter. Epochs of 2 s, from-1000 ms to + 1000 s with respect to the onset of visual cue, were extracted for analyses. The fastICA toolbox in EEGLAB was used for data decomposition, and the artifactual components (e.g., eye movements/blinks) were detected and manually removed based on component time course, topography, and power spectral density [57]. After removing the artifactual components, we visually examined each trial to determine if there were remaining artifacts. Those trials with artifacts were removed. In this study, at least 90% of the trials were clean and saved for analysis. The clean trials were analyzed in the time-frequency domain.

The power decrease at the mu rhythm (i.e., mu ERD) on C3, C4, F3, and F4 channels was examined and represented cortical activation of M1 and PMC of ipsilesional and contralesional hemispheres. The mu ERD was expressed as a percentage power decrease from 0 to 1000 ms after the visual cue (i.e., during key pressing movements) compared to-1000 to 0 ms before the visual cue (i.e., the baseline period) at the mu rhythm. It was calculated as (R-A)/ R. "R" was the power at the baseline period. "A" was the power during the key pressing movements [38]. The ERD of all trials at the C3, C4, F3, and F4 channels was averaged respectively. In addition, to characterize the cortical activation between the ipsilesional and contralesional hemispheres, a laterality index (LI) was also calculated. The LI was expressed as: (iM1-ERD–cM1-ERD)/(iM1-ERD + cM1-ERD) [58]. The LI ranges from – 1 to 1 representing cortical lateralization towards the contralesionsal or ipsilesional hemispheres. A positive increase in LI indicated a shift of cortical activation from the contralesional to the ipsilesional hemisphere and may suggest true neuronal recovery occurred in the ipsilesional hemisphere [58].

Aside from the above EEG indices examined in this study, we also derived the EEG index in the alpha band. The alpha power was investigated to underscore the possible neural mechanisms and their relations to clinical measures. These data were reported [59] and submitted [60].

Statistical analysis

The Shapiro-Wilk test was conducted to examine the normality of all data. Participants' baseline demographics and clinical characteristics were compared using the chi-squared test for the categorical variables and the analysis of variance (ANOVA) for the continuous variables. The paired t-test was used to evaluate changes in all outcomes from pre- to post-intervention within groups. The analysis of covariance (ANCOVA) was used to examine differences of all outcomes between groups with baseline scores as covariates and the Bonferroni correction procedure was implemented for post-hoc analyses. Effect sizes including Cohen's d (for within-group comparison) and the partial eta squared (η^2, for between-group comparison) were computed [61]. An effect size η^2 greater than 0.138 indicated a large effect, η^2 greater than 0.059 indicated a moderate effect, and η^2 greater than 0.01 indicated a small effect [61]. Data were analyzed using SPSS 22.0 (IBM Corp., Armonk, NY). The alpha level was set at 0.05.

Results

Thirty-six participants were enrolled and equally distributed into three groups (PMC, $n = 12$; M1, $n = 12$; Sham, $n = 12$). All enrolled participants completed interventions and clinical and EEG assessments. There were no major side effects of tDCS in the participants. Some participants reported feelings of tingling and itchy at the beginning of each session and these feelings gradually faded away throughout the training sessions. Two participants in the PMC group, two in the M1 group, and one in the sham group refused to participate in the kinematic assessments due to time constraints and worried about visiting the laboratory during the COVID-19 pandemic. There were no significant differences between groups regarding the demographics and baseline clinical characteristics (Table 1).

Table 2 summarizes within- and between-group comparisons of the kinematic and clinical outcomes. For within-group comparison, the index PV significantly increased ($t = -3.85$, $P = 0.004$, $d = 0.72$), and the index MU significantly decreased ($t = 2.7$, $P = 0.02$, $d = 0.77$) with large effect sizes in the PMC group. In addition, significant reductions with a large effect size were also found in the MAS scores ($t = 3.1$, $P = 0.01$, $d = 0.9$) in the PMC group. Significant reductions were found in the trunk TD ($t = 3.26$, $P = 0.01$, $d = 0.41$) and maximal trunk flexion ($t = 3.14$, $P = 0.01$, $d = 0.46$) with medium effect sizes in the M1 group. In contrast, there were significant increments in the trunk PV ($t = -2.61$, $P = 0.03$, $d = 0.26$) and decrements in the trunk MU ($t = 3.78$, $P = 0.004$, $d = 0.8$) and MT ($t = 2.21$, $P = 0.05$, $d = 0.34$) in the sham group with small to large effects.

For between-group comparison, significant differences were found in the index PV ($F_{(2,27)} = 4.19$, $P = 0.03$, $\eta^2 = 0.24$), index MU ($F_{(2,27)} = 3.64$, $P = 0.04$, $\eta^2 = 0.21$), trunk MU ($F_{(2,27)} = 4.13$, $P = 0.03$, $\eta^2 = 0.23$) and trunk TD ($F_{(2,27)} = 3.9$, $P = 0.03$, $\eta^2 = 0.22$), all with large effect sizes.

Table 1 Demographic and clinical characteristics of the participants

Variables	PMC (*N* = 12)	M1 (*N* = 12)	Sham (*N* = 12)	*P*
Age (year)	58.95 ± 12.4	54.33 ± 14.6	64.03 ± 7.25	0.15
Gender (Male/Female)	8/4	11/1	10/2	0.29
Side of hemiparesis (Right/Left)	6/6	6/6	6/6	1
Time since stroke (months)	53.92 ± 39.79	48 ± 42.44	26.33 ± 16.85	0.14
Hemorrhagic/Ischemic Stroke	4/8	8/4	5/7	0.24
FMA-UE	23.58 ± 5.16	23.17 ± 5.54	23.33 ± 6.13	0.39
MMSE	28.33 ± 1.56	28.42 ± 1.73	28.67 ± 1.15	0.85

Note: PMC, iPMC-tDCS with MT group; M1, iM1-tDCS with MT group; Sham, Sham-tDCS with MT group; FMA-UE, Fugl-Meyer assessment scale of Upper Extremity; MMSE, Mini-Mental State Examination. Value is presented as mean ± standard deviation (SD)

Post-hoc analyses revealed that the index PV significantly increased ($P = 0.02$), and the index MU significantly decreased ($P = 0.05$) in the PMC than in the sham group. The trunk TD was significantly reduced in the M1 than in the sham group ($P = 0.04$). The trunk MU significantly declined in the sham than in the PMC group ($P = 0.05$).

Figure 3. illustrates the mu rhythm ERD of the ipsilesional and contralesional M1 and PMC of the three groups. For within-group comparison, the iM1-ERD ($t = -0.09$, $P = 0.05$, $d = 0.45$) and contralesional PMC (cPMC)-ERD ($t = -2.2$, $P = 0.05$, $d = 0.49$) significantly increased with medium effect sizes in the M1 group (Fig. 3a and d). In contrast, the iM1-ERD significantly decreased in the sham group with a medium effect size ($t = 3.95$, $P = 0.002$, $d = 0.68$) (Fig. 3a). There were no changes of iPMC-ERD or contralesional M1(cM1)-ERD in the three groups and no changes of cPMC-ERD in the PMC and sham groups from pre-to post-intervention (Fig. 3b and c).

For between-group comparison, significant differences were found in iM1-ERD between the three groups ($F_{(2,32)} = 4.55$, $P = 0.02$, $\eta^2 = 0.22$) with a large effect size. Post-hoc analysis revealed that the M1($P = 0.04$) and PMC ($P = 0.05$) groups had significantly greater increments of iM1-ERD than the sham group (Fig. 3a). There were no differences in iPMC-, cPMC- and cM1-ERD between groups (Fig. 3b and c).

Figure 4 shows the LI of the three groups. The LI significantly declined with a large effect size and became more negative in the sham group ($t = 2.43$, $P = 0.03$, $d = 0.96$) from pre-to post-intervention intervention. In contrast, the LI was similar between pre-and post-intervention in the M1 and PMC groups.

Discussion

To our knowledge, this study was the first to examine the effect of tDCS on iPMC and iM1 compared to sham stimulation on augmenting effects of MT on motor control, muscle function, and brain activity in chronic stroke. We found differential patterns of improvements in movement performance and motor control strategies, as well as muscle spasticity and brain activation between groups. The PMC group improved paretic upper limb control and muscle function showing increased reaching movement smoothness, greater peak velocity, and reduced muscle spasticity. The M1 group showed mitigation of trunk compensation during reaching with reduced trunk displacements and maximal trunk flexion. By contrast, the sham group used more trunk compensation movements showing greater peak velocity, increased movement smoothness, and reduced movement time of the trunk during paretic upper limb reaching.

The brain activity changes were also different between the three groups. The PMC and M1 groups had a greater increase in iM1 activity than the sham group. In addition, the activity of both hemispheres (i.e., the iM1 and cPMC) increased in the M1 group after interventions. By contrast, the activity of iM1 decreased along with a declined and more negative laterality index showed in the sham group after interventions, suggesting that there might be a shift of cortical activation from the ipsilesional to the contralesional hemisphere after sham tDCS with MT.

Consistent with our hypothesis, we found differential effects of iPMC- and iM1-tDCS with MT on motor control in participants with chronic hemiparesis. Furthermore, we identified different patterns of motor control strategy (i.e., paretic upper limb end-point control vs. trunk compensation) between the iPMC, iM1, and sham groups. The PMC group could move the paretic upper limb faster and smoother, suggesting that a behavioral recovery, rather than compensation occurred after iPMC-tDCS with MT and participants' motor control strategy recovered toward a more normalized pattern (i.e., the end-point control strategy) similar to healthy individuals [48, 49, 62]. In addition, improvements in paretic upper limb control parameters (i.e., greater peak velocity and movement smoothness) indicated that participants could use feedforward control to predict and plan reaching movements before execution after stimulation of iPMC [50, 62, 63]. These results were in line with current evidence showing that PMC is critical for preparing and planning appropriate actions for completing a goal-oriented task, such as the reach-to-target task [64–66]. During the reach-to-target task, the PMC receives integrated

Table 2 Descriptive and Inferential statistics of clinical and kinematic outcomes

Variable	Pre-intervention			Post-intervention			Between-group Comparison			Within-group Comparison								
										PMC			M1			Sham		
	PMC	M1	Sham	PMC	M1	Sham	*F*	*P*	η^2	*t*	*P*	*d*	*t*	*P*	*d*	*t*	*P*	*d*
Clinical Variables	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD												
MAS	0.83 ± 0.34	0.94 ± 0.69	0.67 ± 0.4	0.57 ± 0.23	0.79 ± 0.55	0.55 ± 0.25	1.63	0.21	0.09	3.1	0.01*	0.9	1.77	0.11	0.24	1.57	0.15	0.36
MRC	2.9 ± 0.84	3.08 ± 0.99	3.05 ± 0.85	3.09 ± 0.74	2.76 ± 1.25	3.27 ± 0.88	1.67	0.2	0.1	-1.67	0.12	0.25	0.86	0.41	0.29	-2.09	0.06	0.25
Kinematic Variables																		
Index PV (mm/ms)	605.72 ± 174.73	739.08 ± 181.03	626.35 ± 233.82	752.42 ± 230.39	788.48 ± 257.29	584.86 ± 221.41	4.19	0.03*	0.24	-3.85	0.004*	0.72	-0.85	0.41	0.22	1.07	0.31	0.18
Trunk PV (mm/ms)	138.72 ± 80.03	163.01 ± 97.08	158.13 ± 107.99	165.25 ± 75.38	181.18 ± 144.25	188.22 ± 124.62	0.14	0.87	0.01	-1.63	0.14	0.34	-0.76	0.47	0.15	-2.61	0.03*	0.26
Index MU (unit/mm)	5.43 ± 4.44	5.35 ± 3.92	6.84 ± 11.5	2.85 ± 1.72	3.43 ± 2.61	9.19 ± 18.2	3.64	0.04*	0.21	2.7	0.02*	0.77	2.01	0.07	0.58	-1.13	0.29	0.15
Trunk MU (unit/mm)	3.01 ± 1.32	3.10 ± 1.87	4.53 ± 3.05	2.88 ± 1.29	2.79 ± 1.22	2.52 ± 1.86	4.13	0.03*	0.23	0.33	0.75	0.11	0.63	0.54	0.14	3.78	0.004*	0.8
Index MT (sec)	2.65 ± 2.98	1.77 ± 0.71	3.06 ± 3.15	1.66 ± 0.83	1.43 ± 0.52	2.55 ± 3.08	0.79	0.47	0.06	1.35	0.21	0.45	2.12	0.06	0.55	1.31	0.22	0.16
Trunk MT (sec)	2.91 ± 3.16	2.02 ± 0.79	3.24 ± 2.93	2.03 ± 0.88	1.69 ± 0.74	2.33 ± 2.29	0.06	0.94	0.01	1.07	0.31	0.38	1.75	0.11	0.11	2.21	0.05*	0.34
Index TD (mm/mm)	139.74 ± 44.23	147.22 ± 33.56	159.09 ± 63.51	142.03 ± 39.06	143.79 ± 33.47	158.31 ± 51.05	0.15	0.86	0.01	-0.28	0.79	0.05	0.61	0.56	0.1	0.06	0.96	0.01
Trunk TD (mm/mm)	106.23 ± 86.12	125.52 ± 91.68	137.01 ± 103.2	103.92 ± 72.99	91.03 ± 73.73	139.26 ± 100.71	3.9	0.03*	0.22	0.2	0.85	0.03	3.26	0.01*	0.41	-0.2	0.85	0.02
Max Shoulder flex (deg/mm)	46.81 ± 18.82	38.95 ± 13.99	34.18 ± 15.74	46.16 ± 14.58	36.48 ± 15.6	34.01 ± 15.49	0.45	0.64	0.03	0.27	0.79	0.04	1.78	0.11	0.17	0.06	0.96	0.01
Max Trunk flex (deg/mm)	10.79 ± 8.23	13.28 ± 8.54	13.91 ± 11.14	9.76 ± 6.41	9.64 ± 7.41	14.1 ± 9.97	2.36	0.11	0.15	0.71	0.5	0.14	3.14	0.01*	0.46	-0.11	0.92	0.02

Note: PMC, iPMC-tDCS with MT group; M1, iM1-tDCS with MT group; Sham, Sham-tDCS with MT group; MAS, Modified Ashworth Scale; MRC, Medical Research Council Scale for Muscle Strength; PV, peak velocity; MU, movement units; MT, movement time; TD, Total displacement. Value is presented as mean ± standard deviation (SD).*$P \leqq 0.05$

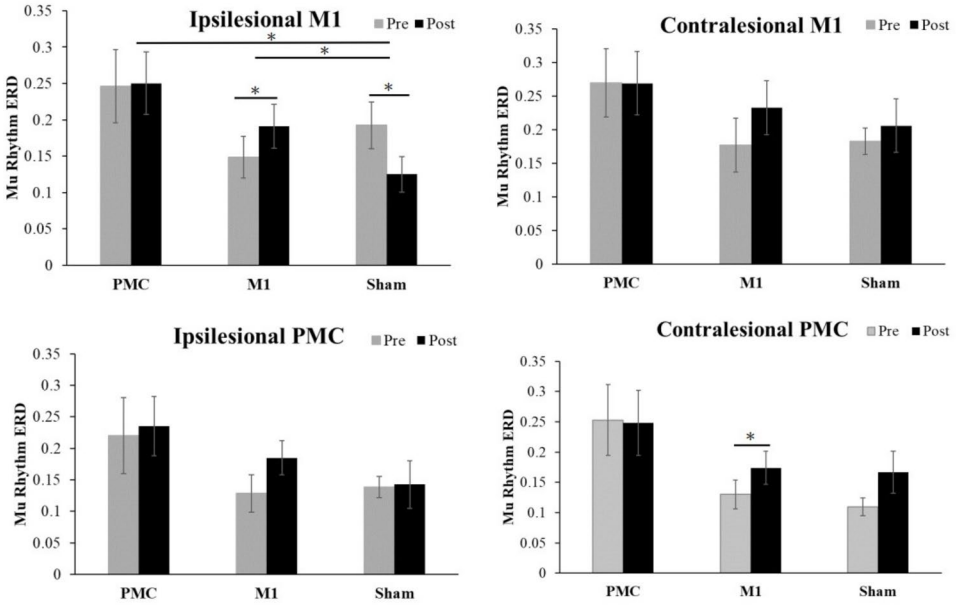

Fig. 3 The mu rhythm ERD of the ipsilesional/contralesional M1 and PMC of the three groups. *$P \leqq 0.05$

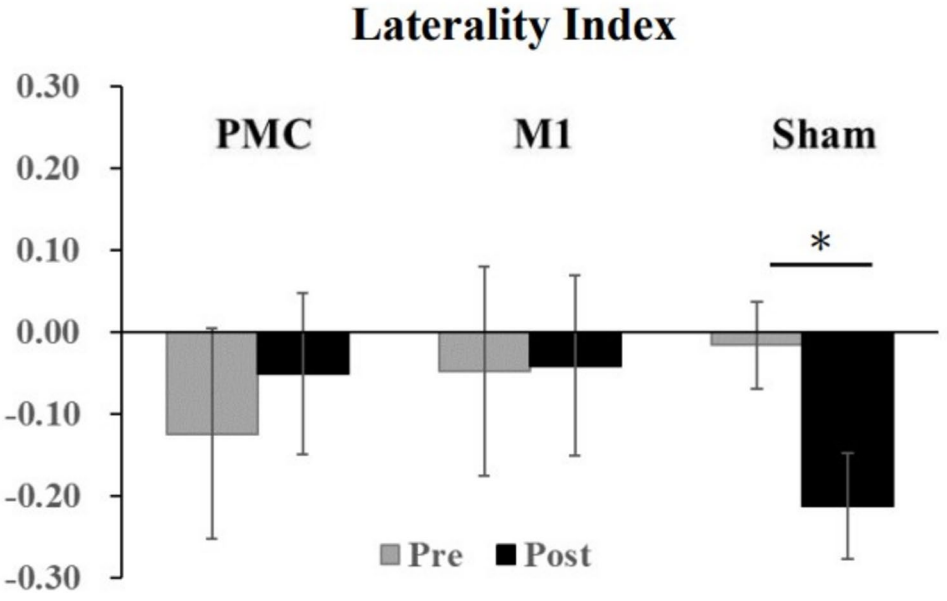

Fig. 4 The laterality index of the three groups from pre- to post-intervention. *$P \leqq 0.05$

visual and somatosensory inputs from the neighboring brain area (e.g., the parietal lobe) to identify the relative position of the body and the target and plans the arm/hand actions and specifies movement parameters (e.g., the trajectory, direction, and speed of upper limb) before movement execution [67–69]. It may be possible that stimulation of iPMC could facilitate these motor preparation and planning processes, and together with the repetitive practice of goal-oriented actions during MT, it could further enhance the restoration of normalized movement patterns of the paretic upper limb [24].

In addition to the motor control improvements, muscle spasticity declined in the paretic upper limb in the PMC group after interventions. Spasticity is a common pathological change in muscle function post-stroke. It is characterized by an abnormal increase in muscle tone, resulting in muscle hypertonia, joint contracture, and restriction of movement [70, 71]. Studies have suggested that spasticity may result from the imbalance between the supraspinal inhibitory (e.g., cortex and corticospinal tracts, CST) drive of the pyramidal system and facilitatory drive (e.g., medial reticulospinal tracts, RST) of the

extrapyramidal system [70, 72]. The supraspinal inhibitory drive may be disrupted by stroke lesions, causing it unable to counter-balance the facilitatory drive and give rise to muscle spasticity [70, 72]. It may be possible that stimulation of iPMC might up-regulate excitability of the pyramidal system, which in turn enhances the inhibitory drive from the lesioned hemisphere to the spinal cord, thus reducing muscle spasticity [72, 73]. However, current evidence of whether tDCS could reduce spasticity is still inconclusive due to the heterogeneous results of the tDCS studies [19, 74]. Various tDCS approaches (anodal or cathodal tDCS) and stimulation targets (iM1 or cM1) were adopted between studies [19]. Our results indicated that anodal tDCS on iPMC might be a potentially effective approach to reduce muscle spasticity in chronic stroke patients. Future studies could combine iPMC-tDCS with spasticity treatments, such as Botulinum toxin to examine if this combination could further augment the effects of stroke spasticity treatments.

The M1 group demonstrated reduced trunk displacements and flexion during paretic upper limb reaching. These results suggested that participants could maintain their trunk posture when reaching a target and the trunk compensation was mitigated after stimulation of iM1 [75]. Trunk compensation is a maladaptive motor control strategy frequently adopted by stroke patients to compensate for deficits in motor control of the paretic upper limb [75, 76]. Overly relying on trunk compensation may hinder functional recovery, cause learned non-use of the paretic upper limb, and induce secondary complications [76, 77]. Several rehabilitation approaches have been developed to reduce trunk compensation, for example, trunk restraint therapy where stroke patients practice task-specific activities with their trunks restrained by harnesses [78]. Our findings demonstrated that iM1-tDCS with MT could be a potentially useful approach to mitigate trunk compensation during paretic upper limb reaching and could be considered incorporated into trunk restraint training to maximize its effects.

Despite the improvements in trunk compensation, the M1 group did not demonstrate changes in the paretic upper limb motor control after interventions. Instead, significant changes were identified in participants receiving stimulation of iPMC. It may be possible that stimulation of iPMC could be the key to optimize recovery of paretic upper limb end-point control while stimulation of iM1 predominantly helped mitigate maladaptive trunk compensation movements [76]. Based on our findings, rehabilitation scientists/therapists could select appropriate brain stimulation targets (e.g., iPMC or iM1) based on the therapeutic goal (i.e., training of paretic upper limb or mitigation of trunk compensation) and combine it with appropriate neurorehabilitation interventions (e.g., MT) to optimize overall treatment benefits.

Another important question of this study is whether brain activity changes would be different between iPMC-, iM1-tDCS, and sham stimulation. As expected, we found differential patterns of brain activity changes between groups. The PMC and M1 groups had significantly greater increments of iM1 activity than that of the sham group. There were no statistical differences in the iM1 activity between the PMC and M1 groups, suggesting that applying tDCS, either on iM1 or iPMC, before MT, could facilitate neuronal recovery of the lesioned cortex. In this study, the improvement in motor control strategies accompanied by the increment of iM1 activity in the PMC and M1 groups indicated that at least some degrees of true recovery had occurred in participants receiving active tDCS (i.e., iM1- and iPMC-tDCS) [49].

To our surprise, the activity of both hemispheres, including the iM1 and cPMC increased in the M1 group after intervention, suggesting that both hemispheres could be modulated by stimulating iM1. These findings were coherent with evidence from previous studies showing that M1 and the contralateral PMC are interconnected through the corpus callosum and can affect one another during movements [79–83]. This increased activation of cPMC after iM1-tDCS may also be one potential reason why trunk compensation was mitigated in participants.

Studies have shown that the contralesional hemisphere (e.g., cPMC) may affect stroke recovery through the ipsilateral tracts [21, 28, 84]. These ipsilateral tracts (e.g., the reticulospinal and anterior corticospinal tracts) are critical for controlling and maintaining body posture [85, 86]. The increased activation of cPMC may facilitate trunk posture maintenance through ipsilateral tracts and lead to reductions in trunk compensation [85, 87]. On the contrary, we did not find trunk performance changes in the PMC group, possibly because there was little modulation of the contralesional hemisphere after iPMC-tDCS.

However, activations of the contralesional hemisphere may not always be beneficial for upper limb recovery post-stroke, especially for patients with milder impairment [88]. The overly active contralesional cortex may cause an imbalance between hemispheres and disrupt paretic upper limb function in these participants [88]. It may be plausible that the increased activation of cPMC after iM1-tDCS may potentially affect paretic upper limb control; as a result, no significant improvements were seen in paretic upper limb kinematics. Nevertheless, we did not find upper limb movement deterioration either, and we observed a trend of potential improvement in index finer movement time ($P = 0.06$), suggesting that iM1-tDCS with MT was still an effective intervention and could be most beneficial for facilitating trunk maintenance/control in stroke patients.

The sham group showed changes only in trunk movements. Participants moved their trunks faster and smoother during the reach-to-target task. These results suggested that the trunk compensation might be strengthened and facilitated after sham-tDCS with MT. In addition, the iM1 activity declined and the LI became more negative in the sham group, indicating a shift of brain activation from the ipsilesional to the contralesional hemisphere after interventions. This finding was coherent with previous studies that found mirror visual feedback (MVF) could modulate the activity of both M1 [89]. Moreover, a recent study found a compensatory increment of cM1 activity and recruitment of ipsilateral pathways in stroke patients receiving 4 weeks of MT [90]. The ipsilateral pathways are critical for controlling proximal and trunk movements. This could be why participants in the sham group demonstrated trunk movement improvements and used trunk compensation in upper limb reaching tasks after interventions. This shift of brain activation accompanied by strengthened trunk compensation strategy suggested that a compensatory recovery might have occurred at the behavioral and brain neuronal levels after sham-tDCS with MT [49].

Three potential limitations should be considered. First, in consideration of the clinical characteristics of the enrolled participants, our findings may apply to chronic stroke patients with moderate-to-mild impairment. Second, we identified brain activity changes between groups; however, it may also be beneficial for future studies to include other types of neurophysiological (e.g., motor invoked potentials or interhemispheric inhibition) or brain imaging assessments (e.g., brain connectivity). This may help provide a comprehensive overview of M1- and iPMC-tDCS effects on neural mechanisms. Third, we could not rule out the possibility that stimulation of iPMC and iM1 may affect one another given the inherent neural connection between these two regions. However, we used a focal electrode (i.e., 3.14 cm^2) rather than the large, conventional electrodes (e.g., 25 or 35 cm^2) commonly used in most previous tDCS studies [91]. Furthermore, we identified distinct effects of iM1- and iPMC-tDCS on motor control, muscle function, and brain activity. Future studies could use advanced current flow modeling toolboxes with tDCS to monitor and guide the direct current flow in the brain [92].

Conclusions

Our study demonstrated differential effects of iPMC and iM1-tDCS combined with MT on recovering motor control, muscle function, and brain activity in individuals with chronic hemiparesis. iPMC-tDCS with MT improved paretic upper limb end-point control and reduced muscle spasticity. iM1-tDCS with MT enhanced trunk maintenance during upper limb movements and mitigated trunk compensation, potentially by upregulating the cross-hemispheric neural network (i.e., iM1 and cPMC). Our study also showed that contemporary neurorehabilitation therapy such as MT alone may facilitate compensatory recovery at behavioral and brain neuronal levels. These findings suggest that both iPMC and iM1 could be effective stimulation targets for improving motor control and brain function in chronic stroke patients. Which one of them should be selected for stimulation may depend on the treatment goal and the needs of the participants. Aside from our findings, further studies could examine whether patients' clinical characteristics, such as lesion sites, would affect their responses to iPMC-tDCS and provide stimulation accordingly. This will facilitate future clinical application of iPMC- tDCS in stroke patients.

Abbreviations

tDCS	Transcranial direct current stimulation
MT	Mirror Therapy
M1	Primary motor cortex
PMC	Premotor cortex
iM1	Ipsilesional primary motor cortex
iPMC	Ipsilesional premotor cortex
cM1	Contralesional primary motor cortex
cPMC	Contralesional premotor cortex
MAS	Modified Ashworth Scale
MRC	Medical Research Council Scale for Muscle Strength
PV	Peak velocity
MU	Movement units
TD	Total displacements
MT	Movement time
EEG	Electroencephalogram
ERD	Event-related desynchronization
LI	Laterality index

Author contributions

WWL completed the manuscript and data analyses. CYL contributed to subject recruitment and training. CYW contributed to developing the study protocol, grant application, project management, and manuscript revision. All authors were involved in the interpretation and revision of this study. All authors read and approved the final manuscript.

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Data availability

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

Declarations

Ethics approval and consent to participate

All participants gave written informed consent before participating in this study. This study was approved by the Institutional Review Board of Chang Gung Memorial Hospital, Taiyuan, Taiwan.

Consent for publication

Not applicable.

Competing interests
The authors declare no competing interests.

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