Theory-Driven EEG Indexes for Tracking Motor Recovery and Predicting the Effects of Hybridizing tDCS With Mirror Therapy in Stroke Patients

Chia-Lun Liu, Ken-Hsien Su, Yi-Shiung Horng, Chia-Ling Chen, Shou-Hsien Huang, and Ching-Yi Wu

***Abstract*— Stroke remains a leading cause of adult disability, underscoring why research continues to focus on advancing new treatment methods and neurophysiological indexes. While these studies may be effective, many lack a clear theoretical framework. The current study first determined the optimal combination effects of mirror therapy (MT) with transcranial direct current stimulation (tDCS) on the premotor or primary motor cortex on its short-term and sustained clinical outcomes. We then introduced electroencephalogram (EEG) indexes derived from the gating-by-inhibition model to explore the underlying therapeutic mechanisms. The EEG indexes used in this study focused on the functional involvement for motor generation: alpha power at temporal regions (inhibiting non-motor activity) and central-frontal regions (releasing motor regions from inhibition). Results showed that post-training benefits, measured by Fugl-Meyer Assessment (FMA), were similar across 3 tDCS interventions (premotor, primary motor, sham). EEG seemed more sensitive to the training, with notable responses in the premotor tDCS group. Three months after training, only the premotor tDCS group maintained the gains in FMA, with these improvements correlated with the EEG indexes. Again, this pattern was specific to premotor tDCS. Since the gating-by-inhibition model suggests that EEG index reflects an individual's psychomotor efficiency, we also found that the baseline EEG index could predict FMA retention. Our findings demonstrate the superiority of combined premotor tDCS with MT and identify functionally oscillatory alpha-band activity in the temporal and central-frontal regions as potentially underlying the therapeutic mechanism. An individual's spatial pattern of EEG may be effective in predicting upper extremity retention effect.**

***Index Terms*— Stroke, EEG, neurorehabilitation, mirror therapy, tDCS.**

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I. Introduction

STROKE remains a leading cause of permanent disability in many countries [1]. Neurorehabilitation approaches and, more recently, neuromodulation techniques play pivotal roles in promoting cortical reorganization, enhancing upper extremity (UE) recovery (measured by tools like the Fugl-Meyer Assessment, FMA), and improving functional independence to maximize patient participation in daily activities [2], [3]. The enhancement induced by neuromodulation could even persist for several months or up to a year [4]. The behavioral improvements observed during neurorehabilitation can be tracked and reflected in electroencephalograms (EEG), which provide a variety of useful indices with previously identified functional roles. Furthermore, EEG indexes have been proposed as a predictive tool for assessing motor recovery after stroke [5]. These studies offer important insights into the therapeutic mechanisms underlying neuromodulation methods. However, many neurostimulation protocols and EEG indexes remain exploratory, lacking a clear theoretical framework. Without a treatment theory, the connection between an index and its underlying mechanism remains ambiguous.

While both mirror therapy (MT) and transcranial direct current stimulation (tDCS) have individually been proven effective [6], [7], recent research has shifted toward an augmentation approach that combines MT with tDCS to further promote neuroplasticity [8], [9], [10]. Mirror illusion is a critical element in mediating MT effects [11]. One study showed that tDCS stimulation of the primary motor cortex (M1) biases the unseen arm towards the reflected arm's position [12]. This directly demonstrates the link between tDCS-induced cortical excitability in M1 and the effect of mirror therapy. This suggests that adding tDCS to MT might boost the effects of MT. Despite evidence of the treatment's effectiveness, identifying the best methods for arm recovery and function remains among the top 10 research priorities for life after stroke [13]. Our focus in this study is on two factors for insights into optimizing the current tDCS protocol: the location of tDCS application and reliable EEG indexes.

One key factor in optimizing the tDCS protocol is the application site. It remains unclear how the site of tDCS application can be effectively and efficiently used in conjunction with motor training (e.g., MT). Equally important is the need to explore how these indexes correlate with the effectiveness of tDCS.

Since the vital role of M1 in movement production and motor control, M1 is one of the most common tDCS application location for patients with stroke. However, M1 is often involved when a stroke occurs. The premotor cortex (PMC) has extensive and independent contributions to the corticospinal tracts; stimulation to the PMC with tDCS could induce robust corticospinal plasticity for motor improvement and therefore has been suggested as an alternative stimulation site for motor recovery [14]. Relating to MT, the PMC is not only part of the mirror neuron system, but also coupled its activation with M1 during MT [15], [16]. Most importantly, the PMC is also known for its role in motor control and learning and cognitive functions [17], particularly in integrating sensory information and selecting appropriate movement parameters for action.

EEG and its derived indexes, such as event-related potentials and frequency domain measures, have been linked to specific functional motor processes [18], [19] and have been used to track improvements in limb function [5], [7]. For instance, the absence of N40 component in stroke patients has been interpreted as insufficient suppression of irrelevant sensory information during balance and mobility tasks [20]. In the same study, this EEG component was also found to be a significant predictor of walking balance performance.

To better understand the therapeutic mechanism with a theory foundation, one can refer back to processes relating to psychomotor efficiency. At the neurophysiological level, the execution of an action is accompanied by a distinct spatial pattern of EEG, particularly reflected in oscillatory activity at the alpha band. The gating-by-inhibition model explains how a motor is executed by activating motor regions while inhibiting non-motor regions through alpha power modulation [21]. The function of alpha is to exert inhibitory control across the cerebral cortex; therefore, an efficient motor generation require higher alpha (inhibition) on non-motor regions (temporal) and less alpha (release from inhibition) on motor related regions(central) [21], [22]. Moreover, studies have also found that alpha power collected at central and temporal regions (EEG 10-20 system) can reflect improvements in psychomotor efficiency with practice [23] or motor performance [24]. These results demonstrate that practice or training can affect the alpha gating system to redirect neural resources more efficiently toward processes that support performance and away from those unrelated to performance. Compared with M1, the functional roles of the PMC appear to more fit the gating-by-inhibition model and thus the relevant EEG indexes associated the model could be leveraged to explore the therapeutic mechanism. Together, these results not only imply that EEG indexes derived from the alpha gating model could reflect neuroplasticity but also provide new insights into the therapeutic mechanisms behind different tDCS mentioned earlier.

Currently, research exploring the impact of combined tDCS-MT with EEG is scarce. A few studies have investigated resting-state oscillatory phase coupling networks in stroke patients, revealing that connectivity in the PMC and M1 in the alpha band can predict motor recovery [25], [26]. Our recent study, based on the current project, tested the role of alpha power using the gating-by-inhibition model and found a strong correlation between alpha power and daily activities following premotor tDCS [27]. However, direct evidence linking alpha power in the temporal region, associated with inhibition of non-motor function, to basic motor functions remains unknown. Based on these findings, the goal of motor training and other neurorehabilitation approaches for stroke patients is to relearn lost motor functions. Enhancing PMC activity with tDCS could facilitate motor learning processes and help assess the functional relevance of EEG index derived from theoretical models.

The aims of the present study were threefold. Our first aim was to confirm the augmentation effects of the combined tDCS with MT treatment by comparing the FMA, between the PMC, M1, and Sham tDCS at three time points: pre-training, post-training, and follow-up. We expect that such combination of tDCS and MT will effectively improve motor recovery immediately after training (i.e., post-training effects). The improvement would be pronounced in the PMC and/or M1 group. Additionally, we tested the sensitivity of neurophysiological EEG indexes derived from the gating-by-inhibition model with the post-training effects. This was tested by directly comparing the EEG indexes, including alpha power at central area, temporal area, and the ratio of the two, between the 3 tDCS groups. Moreover, as the PMC has been known for its role in motor control and learning in cognitive function, thus, we anticipate the effect of the PMC tDCS would be evident on the EEG indexes.

The second aim of the study focused on the sustained motor recovery associated with the combination of tDCS and MT approach. The PMC is known to play a key role in compensating for functional loss when the M1 is injured, owing to its extensive and independent contributions to the corticospinal tract. Because of this, rewiring these connections might require more time, as the PMC is also involved in motor planning

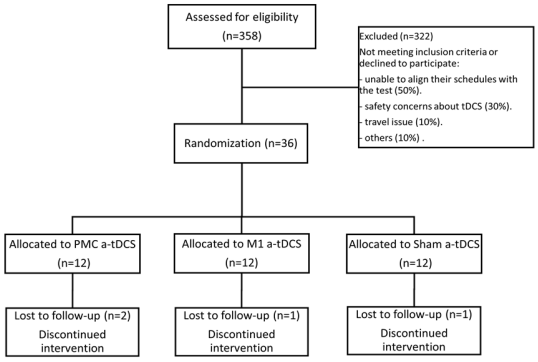

Fig. 1. Consort patient flow chart.

and goal-oriented movements. Consequently, we hypothesized that the PMC stimulation, compared to the M1 and the Sham tDCS, would show greater retention, as assessed three months later. Following the gating-by-inhibition model, we further explored the relationship between behavior and neural activity by examining the correlation between relevant EEG indexes (alpha power at temporal and central regions: post-training vs. pre-training) and sustained motor improvement (follow-up vs. pre-training). By examining these correlations, we aim to link key elements of the gating-by-inhibition model with the clinical outcome of the combined tDCS and MT method, providing empirical evidence to support its use as an adjunct therapy.

As suggested by the gating-by-inhibition model that the distribution of alpha activity might indicate individual baseline psychomotor efficiency, we directly test if the pre-training topography of alpha could be predictive of later-stage functional improvement. Hence, the third aim of this research was to further explore the potential of EEG indexes in predicting functional improvement. We used a linear regression model, incorporating alpha power from central and temporal regions, to assess its potential as a predictor for functional recovery.

Since the exact contributions of the alpha power at different brain areas remains unclear in stroke patients and their relationships with three tDCS interventions are also largely unknow, some of our analyses adopted an exploratory approach. Please note that the effects of the tDCS interventions on muscle function and conventional EEG indexes (e.g., event-related desynchronization), based on the current project, have been assessed in a separate submission. A brief summary of these results is provided in the supplementary material.

II. Methodology

A. Patient Population

A total of 36 qualified patients with stroke were recruited (Fig.1). They were recruited from Taipei Tzu Chi Hospital and Taipei Chang Gung Memorial Hospital in Taiwan. The inclusion criteria were: (1) an age range from 45 to 85 years; (2) Fugl-Meyer assessment (FMA) scores between 18 and 56, indicating moderate to mild impairments; (3) a documented history of unilateral stroke occurring at least 6 months prior to enrollment; (4) with adequate cognitive function to comprehend and adhere to study instructions (the Mini Mental State Examination$\geq$24). Individuals were excluded from participation if they met any of the following criteria: (1) had Botulinum toxin injections in the past 3 months; (2) the upper limbs had excessive muscle tension or joint contracture; (3) concurrent presence of other neurological disorders (e.g., Parkinson's disease, multiple sclerosis) or any mental disorders (e.g., depression); (4) a history of substance use disorder; (5) unstable cardiovascular conditions (untreated hypertension or heart failure); (6) presence of contraindications to undergoing tDCS, including epilepsy history, possession of a pacemaker, existence of metallic implants within the body, brain surgery history etc. [28]; (7) pregnancy; (8) existence of trauma, brain tumor, or arteriovenous malformation at the site of the stimulation; (9) ongoing involvement in other concurrent research projects. All the participants were given detailed information regarding the experimental design, research purpose, and possible risks of the study before signing the consent form.

B. Design

This is a randomized, double-blinded, placebo-controlled clinical trial (ClinicalTrials.gov ID: NCT04655209) designed with pre-training, post-training, and 3-month follow-up tests. At 3 months after the post-treatment (follow-up test), only clinical assessment was conducted. One independent evaluator, blinded to the group allocation, evaluated all outcome measures. The clinical measure, together with EEG physiological recording took about 90 minutes.

The participants were first stratified by the severity of their motor impairment (mild FMA: 41-56 to moderate FMA: 18-40) [29] and brain damage side (right vs. left cerebrovascular disease). Eligible participants in each stratum were randomly assigned to 1 of the 3 tDCS intervention groups: M1 tDCS before MT (M1 tDCS group), PMC tDCS before MT (PMC tDCS group), and sham tDCS before MT (Sham tDCS group). This assignment was conducted by an additional graduate student using a web-based randomization tool (freely available at http://www.randomizer.org/) [30]. To maintain the blinding of the stimulation protocol during treatments, this person sent the patient's group label to the person responsible for tDCS administration and separately sent the patient's contact information to the therapists.

Before this study, no research had examined the relationship between alpha power and physical function in stroke patients. Therefore, our sample size estimation is based on a study [31] that adopted a very similar design in terms of tDCS and training protocol to our current study. One of their outcomes also included FMA and detected a post-training improvement with a sequential combination of tDCS and MT. Based on the previously reported effect size, with a power of 0.8 and an alpha value of 0.05, our sample size estimation suggested that at least 11 participants per group were needed.

C. Experimental Procedure

The participants of the PMC group first received tDCS over the ipsilesional PMC, without any active arm practice for 20 minutes, followed by a 20-mins MT training. The

procedure for the M1 tDCS and the Sham tDCS groups were identical as the PMC tDCS group, except that tDCS was applied on ipsilesional M1. All participants received the MT intervention 90 minutes/day, 5 days/week, for 4 consecutive weeks. The time interval between the first and last intervention session and pre- and post-training assessments was within 4 days. A mirror was placed in participants' sagittal plane during MT. Participants were required to look at the reflection of non-paretic arm in the mirror, imagined it as the paretic arm and performed bilateral arm movements as simultaneously as possible. The MT training consisted of (1) intransitive movements, including distal and proximal arm/hand movements such as wrist extension-flexion, forearm pronation-supination and elbow flexion extension, and (2) transitive movements, such as placing pegs in holes or flipping a card [32]. The amount of time exposed to intransitive and transitive movements was balanced for each participant. The participants practiced 30 intransitive and 30 transitive tasks over the 20 training sessions, and the actual movements were selected based on each individual's need. After 40 minutes of MT, the participants received 30 minutes of functional task training, focusing on tasks that were challenging for them to perform. The functional tasks involved meaningful daily activities with either hand or with both hands, such as grasping a cup with the paretic hand, wringing out water from a wet towel with both hands, or stabilizing a bowl with the paretic hand and scooping food with the non-paretic hand.

During the EEG acquisition, the participants were instructed to press the corresponding keys in response to the direction of the arrow on the screen. If the arrow pointed to the left, the participants then were asked to press the space bar. If the arrow pointed to the right, the participants were asked to press "0" on the keypad. EEG recording was administered only in pre- and post-training and was conducted before clinical assessment.

D. tDCS Protocol

tDCS was administered using a battery-powered direct current stimulator (StarStim, Neuroelectrics, Barcelona, Spain) with two saline-soaked sponge electrodes. The anodal electrode was positioned over the ipsilesional M1 (C3/C4 of the international 10-20 EEG electrode system), while the cathodal electrode was placed on the contralesional FP1/FP2. For the PMC group, the anodal electrode was positioned 2.5 cm anterior to C3/C4 on the ipsilesional PMC, with the cathodal electrode still placed on FP1/FP2. For M1 tDCS, the anodal electrode was aligned parallel to the central sulcus [17]. The electrodes were secured with Velcro bands. The size of the electrodes was 3.14 cm^2, and the stimulation intensity was 2 mA, resulting in a current density of 0.06 A/m^2 [32], which was well within the current safety limit [33]. For the Sham tDCS, stimulation was ramped up to 2 mA over 15 seconds, then gradually reduced to 0 over the next 30 seconds [17]. This method has been shown to be efficient for blinding patients [35].

The tDCS protocol used in this study (2 mA of anodal tDCS for 20 minutes) was developed based on following considerations. First, anodal tDCS has been shown to produce a more consistent modulation effects than the cathodal tDCS [36]. Second, in stroke patients, anodal tDCS has been used with stimulation durations ranging from 10 to 30 minutes and intensities between 1 and 2 mA [37], [38]. Studies have also demonstrated that 2 mA of anodal tDCS for 20 minutes is effective in enhancing cortical excitability and generating long-lasting effects [39], [40]. Third, previous research on combining tDCS with upper limb rehabilitation typically used between 14 and 30 training sessions [37], [38], leading us to select 20 sessions for our protocol. Finally, one study systematically investigated the timing of applying tDCS before, during, or after a robotic arm training in patients with stroke and found improvement was pronounced when tDCS was provided before the training [41]. Based on this, we chose to apply tDCS prior to mirror therapy to optimize treatment outcomes.

E. EEG Acquisition and Preprocessing

Continuous EEG was recorded with a cap with 32 flat act-iCAP electrodes (Brain Products GmbH, Gilching, Germany) placed according to the international 10–20 system, with a sampling rate of 500 Hz. The forehead was chosen as ground and mastoids were used as the reference. Four additional electrodes were placed on the face to record horizontal and vertical eye movements. The horizontal electro-oculogram was recorded from electrodes placed at the outer canthus of each eye and the vertical electro-oculogram from electrodes placed above and below the left eye. The EEG was amplified with BrainVision LiveAmp (Brain Products GmbH, Gilching, Germany), and impedances were kept below 5 Ω.

Together with the EEG data recording, a pair of electrodes on each upper arm were attached to acquire the electromyographic (EMG) signals. The EEG reference was placed anterior to Fz and the ground posterior to Pz [42]. To provide a reference point for the start of the movement, the EMG electrodes were placed on the biceps and triceps of the upper arms to record EMG activity.

EEG data was processed offline using EEGLAB [43] and generally followed past preprocessing pipeline [43]. First, all the signals were digitally filtered to 0.5-40 Hz and line noise was removed using CleanLine (cleanline function in EEGLAB, Computational Neuroscience Laboratory, Salk Institute, California). To track motor recovery, we focused on the trials that used the damaged limb (contralateral to the damaged side of the brain) for responses. Epochs were cut from -1.0 to $+1.0$ s relative to response initiation, which was contralateral to the lesion hemisphere. A minimum of 50 artefact free epochs was used for further analyses in every participant. Filtered data then re-referenced to linked mastoids. Physiological noise such as eye movements and blinks were removed through Independent Component Analysis (ICA, "pop_runica" function in EEGLAB), which resulted in an averaged removal of 2.3 components per participant.

F. Clinical Outcomes

The primary focus was on the Fugl-Meyer assessment scale of upper extremity (FMA-UE). FMA-UE was used to evaluate upper limb sensorimotor function in individuals' post-stroke [45], [46]. This assessment involves 33 movements

rated on a 3-point ordinal scale, with a total score range of 0-66. Higher scores reflect less impairment in the affected arm. The FMA has demonstrated good to excellent validity and reliability in stroke populations [47], [48]. Additionally, we used three FMA subscales pertinent to our intervention: FMA-Wrist (5 items; score range 0–10), FMA-Hand (finger and grasp movements; 7 items; score range 0–14), and FMA-Coordination (five repetitions of the finger-to-nose test; 3 items; score range 0–6). Since this study also collected other clinical outcomes and kinematic data, these outcome measures and results were explained and reported in Supplementary material.

G. EEG Indexes

Time-frequency decomposition was performed through wavelet transform method conducting on overlapping windows, each with range from −1 to 1 s relative to response onset. The padratio was set to 4. This procedure was repeated on each channel individually. The yield complex-valued results were first was doubled for all positive frequencies, and alpha power was computed as the squared amplitude in the 8–12 Hz frequency range [21]. Next, we computed absolute alpha power without baseline correction by applying median-scaled log transformation [$10 \cdot \log^{10}$] to each participant.

We first inspect the power spectrum plot for alpha power reduction at central and alpha surge at temporal sites around the onset of response (supplementary data). To solve the issue of the multiple comparison problem, the time windows used to quantify the alpha power at central and temporal sites was first explored through a nonparametric statistical test [49]. This method first repeatedly drew subsets from a combined data set and calculated test statistic from this random partition. The p-value was generated based on the histogram, the proportion of random partitions, to conclude if the experimental conditions were significantly different. This testing could guide meaning cluster of time window for later stage of parametric statistical analyses. Two time-window of clusters were identified with significance: -65-0 and 0-127 ms; the alpha power values within these two windows were targeted for further statistical analyses. For the predictive analysis, two time-windows were identified (-200-0 ms, 100-250 ms) from the spectral perturbation plot at pre-training and previous relevant studies [23], as these two time clusters presented pronounced alpha increase at temporal area and alpha reduction at central. Central-frontal alpha power were averaged across: frontal (F3,Fz,F4), central (C3,CP1,C4,CP2) while temporal alpha power were averaged from: bilateral temporal (T7,F7,CP5,T8,F8,CP6). Alpha frequency range was chose based on past relevant studies [22].

H. Statistical Analysis

Kolmogorov-Smirnov test and Levene's test were applied to test for normality and homogeneity of variance on all behavioral variables. If the normality assumption was violated, between-group comparison was performed using the Kruskal-Wallis Test, and within group comparison was performed using the Friedman test. For normally distributed data, two-way mixed model analysis of variance (ANOVA) with factors of Groups (PMC, M1, Sham), Training (pre- vs. post-training vs. follow-up) was used to examine the effects of stimulation intervention on FMA and relevant EEG indexes. If the 3-by-3 interaction of the ANOVA survived, we then conducted separate ANOVA with the same Group factor but different Training factor (pre- vs. post-training and pre-training vs. follow-up). For each separated mixed ANOVA, post-hoc comparisons with the Tukey's Honest Significant Difference (HSD) test ($\alpha = 0.05$, comparisons $= 3$) were conducted if the 3-by-2 interaction was significant. Effect sizes were measured using partial eta square (η^2) Consistent with our previous results and Cohen, η^2 greater than 0.138 represented a large effect, greater than 0.059 represented a moderate effect, and greater than 0.01 represented a small effect [50]. For measures with follow-up session, if the main effect or interaction survived, planned post-hoc comparisons focused on the difference between baseline and follow-up sessions. Pearson (R) analyses was used to determine the relationship between the neurophysiological indexes and clinical measures. For ordinal scales, the Spearman correlation was used. A linear regression analyses was performed to develop a linear regression model for predicting sustained recovery (FMA scores: follow-up vs. pre). The regressors included alpha power values at temporal and central areas at pre-training session and were all demeaned to reduce the potential of multicollinearity. All the above statistical tests and the regression model were conducted by MATLAB and Statistics and Machine Learning Toolbox 2019b (The MathWorks, Natick, MA, United States).

TABLE I
DEMOGRAPHIC AND CLINICAL FEATURES OF THE PARTICIPANTS

Variables	PMC (n=12)	M1 (n=12)	Sham (n=12)	*p*-value
Age (year)	58.95(12.40)	54.33 (14.60)	64.03 (7.25)	0.22
Gender/Male	8 (66.67%)	11 (91.67%)	10 (83.33%)	0.29[a]
Education (year)	13.75(2.01)	13.25 (4.81)	11.67 (3.28)	0.12
Lesion/left hemisphere (%)	6 (50%)	6 (50%)	6 (50%)	1.00
The time since stroke (months)	53.92(39.79)	48.00 (42.44)	26.33 (16.85)	0.24
MMSE	28.33(1.56)	28.42 (1.73)	28.67 (1.15)	0.94
FMA-UE	23.58(5.16)	23.17 (5.54)	23.33 (6.13)	0.97

Values are mean (standard deviation) or n (%). Categorial variables were tested with Chi-square test (p-value with a) while continuous variables were tested by Kruskal-Wallis test (for non-normalized data). PMC=premotor tDCS, M1=primary motor tDCS, Sham=sham tDCS, MMSE=Mini-Mental State Examination, FMA-UE=Fugl-Meyer Assessment-Upper Extremity.

III. RESULTS

A. Demographical Features

As shown in Table I, there were no significant discrepancies in baseline demographic attributes ($p > .05$ for all), indicating that the groups were well-matched across the three groups on all demographic attributes.

B. Clinical Outcomes

Functional recovery through combined tDCS-MT was assessed using various sections of the FMA (Table II),

TABLE II
CLINICAL OUTCOMES FOR TRAINING EFFECTS

Outcome	PMC tDCS			M1 tDCS			Shame tDCS			P value (interaction)
	Pre	Post	Follow-up	Pre	Post	Follow-up	Pre	Post	Follow-up	
FMA-UE	23.58(1.49)	26.58(1.29)	25.80 (1.36)	23.17(1.60)	25.00(1.79)	21.64(3.62)	23.33(1.77)	26.50(1.89)	17.36(3.91)	0.03
FMA-Hand	2.83(0.84)	3.33(0.85)	3.10(1.05)	3.17(1.04)	4.17(1.10)	3.73(1.12)	4.25(1.18)	5.92(1.34)	4.00(1.61)	0.66
FMA-Wrist	2.33(0.85)	2.50(0.91)	2.00(0.94)	2.58(0.94)	3.08(1.04)	3.73(1.18)	3.08(0.80)	4.67(1.07)	3.64(1.23)	0.24
FMA-Coord.	3.67(0.54)	3.83(0.42)	3.60(0.58)	4.25(0.28)	4.17(0.34)	3.36(0.56)	3.92(0.31)	3.75(0.41)	3.09(0.64)	0.71

Values are mean (standard deviation). PMC=premotor. M1=primary motor. FMA-UE=Fugl-Meyer Assessment-Upper Extremity. Coord.=coordination. The p value indicates the interaction of Group*Training.

focusing on FMA-UE, FMA-Hand, FMA-Wrist, and FMA-Coordination (detailed please see supplementary information Fig. S1). Each section was designed to assess different aspects of motor recovery, thus separate two-way (3-by-3) ANOVA were conducted. For FMA-UE, the interaction of Group*Training was significant ($F(4,58) = 2.79$, $p = 0.034$, $\eta^2 = 0.16$). This permitted the followed-up separate 3-by-2 mixed ANOVA with distinct time frames for the two hypotheses. First, for immediate training effect, the 3-by-2 mixed ANOVA revealed an insignificant interaction ($F(2,33) = 1.09$, $p = 0.35$, $\eta^2 = 0.06$) and a significant main effect of Training was observed ($F(1,33) = 44.15$, $p < 0.01$, $\eta^2 = 0.57$). This indicates an overall improvement in UE in every tDCS group, which was confirmed by significant post-hoc comparisons (HSD test: PMC: $q = 6.10$, $p < 0.01$; M1: $q = 3.73$, $p = 0.02$; Sham: $q = 6.44$, $p < 0.01$). Second, for sustained training effect, a 3-by-2 mixed ANOVA revealed a significant interaction of Group*Training ($F(2,29) = 3.60$, $p = 0.04$, $\eta^2 = 0.19$). Planned post-hoc analyses revealed a substantial improved UE between baseline and follow-up sessions in the PMC (HSD: $q = 4.98$, $p < 0.01$) but a noticeable drop of UE in the Sham ($q = 3.65$, $p = 0.03$). No UE difference was observed in M1 tDCS ($q < 1$, $p = 0.55$). The Training main effect was not significant ($F(1,29) < 1$, $p = 0.37$, $\eta^2 = 0.03$).

For FMA-Hand, the 3-by-3 mixed ANOVA found insignificant interaction of Group*Training ($F(4,58) < 1$, $p = 0.66$, $\eta^2 = 0.04$). The main effect of Training was significant ($F(2,58) = 3.33$, $p = 0.04$, $\eta^2 = 0.10$). The Group effect was not significant ($F(2,29) = 1.12$, $p = 0.34$, $\eta^2 = 0.07$). Since the 3-by-3 interaction was not significant, the separate 3-by-2 mixed ANOVA was not performed. For FMA-Wrist, we found insignificant interaction of Group*Training ($F(4,58) = 1.43$, $p = 0.24$, $\eta^2 = 0.09$) but found a marginal main effect of Training ($F(2,58) = 3.00$, $p = 0.057$, $\eta^2 = 0.09$). The main effect of Group was not significant ($F(2,29) < 1$, $p = 0.57$, $\eta^2 = 0.04$). For FMA-Coordination, similarly, the interaction of Group*Training was not significant ($F(4,58) < 1$, $p = 0.71$, $\eta^2 = 0.04$). The main effects both were insignificant: Training ($F(2,58) = 2.69$, $p = 0.08$, $\eta^2 = 0.09$) and Group ($F(2,29) < 1$, $p = 0.83$, $\eta^2 = 0.01$).

Apart from the FMA-UE, we also explored measures related to quality of life, dexterity, self-efficacy, functional performance, and kinematic performance. While these measures may not be directly relevant to alpha power, we have briefly reported the results in the supplementary information for exploratory purposes. In summary, similar to the FMA-UE, no group difference was observed after the training in any of these measures (interactions were all insignificant).

C. Neurophysiological Outcomes-Alpha Ratio, Alpha Surge, and Alpha Reduction

Psychomotor efficiency relating to functional recovery was evaluated through EEG topography with the alpha ratio (Fig. 2). We applied separate 2-way mixed ANOVA to the alpha ratios prior and after response initiation. Notably, there was a significant interaction of Time*Groups ($F(2,33) = 4.37$,

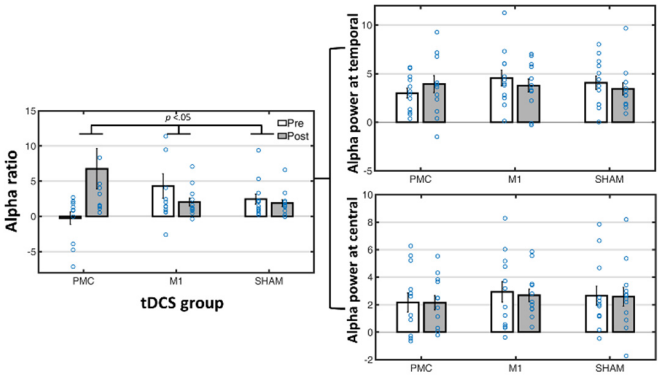

Fig. 2. Alpha power contrasting values between temporal and central regions averaged from time window after response onset. PMC=premotor tDCS, M1=primary motor tDCS, SHAM=sham tDCS. Pre=pre-training, Post=post-training. The error bars are SEM. The blue open circles indicate individual data.

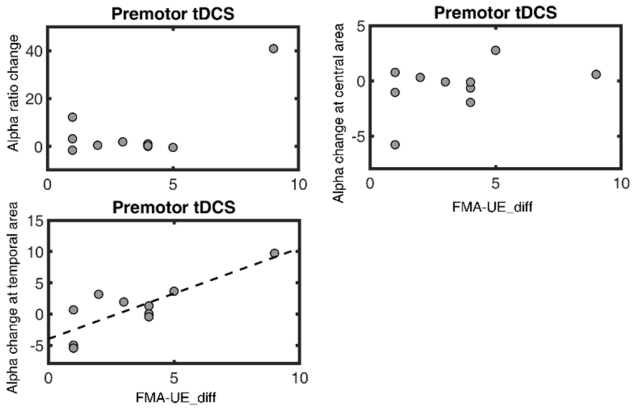

Fig. 3. Scatterplots showing the relationships between the changes of alpha ratio, alpha power at temporal, central regions and the FMA-UE in premotor tDCS group. The dotted line stands for the best linear fit to the data. FMA=Fugl-Meyer Assessment. UE=upper extremity.

$p = 0.02$, $\eta^2 = 0.20$) in the time window of after response onset, which was mainly explained by an enhancement (better psychomotor efficiency) exclusively in the PMC group ($q = 3.67$, $p = 0.02$) but not in the other groups (M1: $q = 1.41$, $p = 0.34$, Sham: $q < 1$, $p = 0.81$). On the other hand, this pattern was not seen in the time window before response (interaction: $F(2,33) < 1$, $p = 0.39$, $\eta^2 = 0.05$). All the main effects from the two time-windows were not significant (all $ps > 0.09$).

To further determine the distinct contributions of the alpha ratio, focusing on the time window after response, we repeated the same ANOVA analyses on alpha power values collected from the temporal area (alpha surge) and central area (alpha reduction). The results (Fig. 4b) revealed an insignificant interaction of Time*Groups in the temporal area ($F(2,33) = 2.68$ 1, $p = 0.083$, $\eta^2 = 0.14$) and an unreliable interaction in the central area ($F(2,33) < 1$, $p = 0.97$, $\eta^2 < 0.01$). Besides, all the main effects were not reliable ($ps > 0.72$).

D. Correlation Between Alpha Ratio and Clinical Measures

To establish the relevance between behavioral improvement and EEG indexes derived from the gating-by-inhibition model, we correlated the changes of alpha power values (pre vs. post) and FMA-UE (pre vs. follow-up), both of which exhibited considerable improvement. In the PMC group (Fig. 3), the sustained improvement of FMA-UE was not related to the change in alpha ratio ($\rho = -0.03$, $p = 0.93$), despite a previously reported significant interaction in the alpha ratio. Further analyses breaking down the alpha ratio into alpha surge and alpha reduction found a robust correlation between alpha surge and behavioral improvement ($\rho = 0.65$, $p = 0.04$), but no relationship between alpha reduction and FMA-UE ($\rho = 0.35$, $p = 0.32$). This clearly suggests that individual with more cortical suppression in temporal area showed larger sustained UE improvement. Finally, these patterns were not observed in the M1 tDCS or the Sham tDCS groups (all $ps > 0.18$), indicating the specificity of the effect for the PMC stimulation.

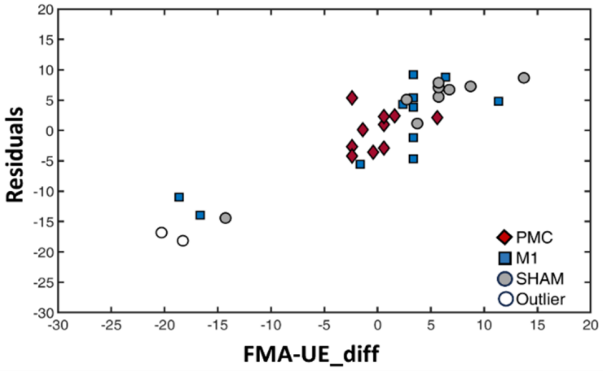

Fig. 4. The scatter plot of the residuals and the FMA-UE change. Unfilled circles represent outliers. FMA=Fugl-Meyer Assessment. UE=upper extremity. diff=follow up – pre-training. PMC=premotor tDCS, M1=primary motor tDCS, SHAM=sham tDCS.

E. Prediction of Alpha Power on Sustained FMA-UE Improvement

As alpha power has been found to correlate with FMA-UE, we further tested if baseline individual alpha power could predict the improvement 3 months later. A multiple linear regression model was constructed with predictors of the alpha power at the temporal and central areas collected at pre-training. Data from the three tDCS groups at the pre-training was included. After removing three outliers identified in the initial results, we repeated the regression analysis. The results of the regression model suggested that an individual's improvement in FMA-UE measured three months later can be significantly predicted by baseline EEG indexes ($R^2 = 0.23$, $p = 0.03$, Fig. 4). Also, these results were not biased toward any tDCS group as the residuals ranged quite similarly between the three tDCS groups. Additionally, we explored alternative regression models by adding extra regressors, such as SIS or demographic features [51], but none of them could predict FMA-UE anymore. This implies that the neurophysiological indexes rather than demographic features are the core elements in predicting FMA-UE.

IV. Discussion

This study aimed to evaluate the immediate and sustained effects of combining tDCS with MT on clinical outcomes. Additionally, we sought to link the EEG measures derived from the gating-by-inhibition model to the clinical improvements observed in earlier research. Our findings showed that when tDCS was combined with MT, the immediate benefits across the PMC, M1, and sham stimulation (MT only) were similar. All the three tDCS groups showed improvement in FMA scores, though the Sham group experienced greater gains in FMA-Wrist and FMA-Hand. The EEG indexes appeared to be more sensitive to the training, as indicated by a higher alpha ratio in the PMC group. Unlike the uniform improvements in FMA-UE across the three tDCS groups after training, the PMC group maintained these gains three months post-training, while other FMA subscales showed the opposite pattern in the M1 tDCS and the Sham tDCS groups. In terms of retention effects, the relationship between behavioral and neural outcomes was tighter in the PMC group, supported by significant correlations between FMA-UE and alpha ratio, as well as between FMA-UE and alpha surge. These correlations were not observed in the M1 tDCS and the Sham tDCS groups. Finally, by demonstrating an association between EEG indexes and FMA-UE, we explored the potential for individual baseline psychomotor efficiency to predict FMA-UE using a multiple linear regression model. The model indicated that alpha power in temporal and central regions could be a reliable predictor of motor recovery. In summary, oscillatory activity in the alpha band, especially in the temporal and central areas, not only correlates with short-term (five-week) upper extremity improvements but may also serve as a simple and specific neural index for predicting sustained (three-month) upper extremity recovery.

Applying tDCS to M1 and PMC with MT each has been shown to be effective in improving various aspects of motor function, respectively [11], [52], [53], [54]. To the best of our knowledge, none of any study directly compares the M1 and PMC tDCS. Our results suggest distinct functional improvements in the PMC and M1 groups (Fig. 2). Surprisingly, the Sham tDCS group (MT only) showed enhancements in most FMA sections. First, it confirms the robustness of the MT in the recovery of motor functions [32]. Additionally, it could result from the possibility that more time is required for the tDCS to integrate its effect with MT. This can be partially supported by the results of sustained improvement in FMA-UE observed three months post-training.

Our sustained improvement was found in the motor function domain (FMA-UE), which may be partially due to the attrition issue; however, this is consistent with findings from a past study with multiple tDCS treatments [4], [55]. Bornheim et al. [4] found that improved functional recovery of the Wolf Motor Function Test could be maintained for up to a year. Besides, sections of FMA were also reported to be detectable after three months post-stroke.

In our study, we found that the improvement in FMA-UE correlated with and alpha surge in the temporal region, but not with other FMA subscales. This may imply that the combination of tDCS on the premotor cortex and mirror therapy could initiate changes from the proximal part requiring more time to become apparent. This explanation sheds light on why we did not observe an immediate improvement after the last treatment.

One primate study compared the corticoreticular connections between the primary motor cortex (M1) and the supplementary motor area (SMA) and found that reticulospinal cells received inputs from broad areas of both regions. Importantly, they found that the corticospinal projection from the SMA was higher than that from M1 [56]. This suggests that the extensive connections in the secondary motor cortex may be utilized for compensation, particularly when M1 is damaged, by exploring effective descending pathways.

We introduced the gating-by-inhibition theory to explain the augmenting effect of tDCS, and a considerable improvement was observed three months after the last treatment in the PMC tDCS group. Based on the correlation and the EEG analyses, it seems that temporal alpha may be involved in upper extremity recovery, although temporal alpha did not significantly differentiate between the three tDCS groups. Here, we provide two possible explanations for the therapeutic mechanism. First, the temporal region, particularly the superior temporal sulcus, has been implicated in the mirror-neuron system [57], which is closely associated with mirror therapy. One straightforward explanation is that tDCS may facilitate motor production by enhancing activity in the premotor region, which then extends its influence to the temporal region. This idea is supported by previous studies showing extensive functional connectivity between the temporal mirror neuron system and the motor cortices, which plays a role in imitation [58]. However, one limitation posed by the EEG method is that the signal from an EEG electrode is not necessarily linked to the brain region directly beneath it. The precise directional influence between these two regions still requires more rigorous testing using a causal method.

Another possibility is that stroke patients are still in the process of neural rewiring, which might not necessarily involve previous motor-related memory or knowledge during rehabilitation. Heightened alpha power could serve to inhibit cognitive functions within the temporal lobe, redirecting patients' limited resources toward establishing new motor networks for movement. This aligns with the alpha gating theory, which suggests that suppressing cognitive interference in the temporal lobe benefits psychomotor efficiency. In the context of stroke rehabilitation, this suggests that effective treatment not only requires stimulating the lesion region but also inhibiting sources of potential interference. The current findings also help explain why the results of the M1 tDCS were mixed. Successful rehabilitation might not solely depend on boosting cortical activity in motor-related regions; it also requires sufficient inhibition of non-motor regions. Future studies could explore manipulating the level of inhibition in the temporal lobe to determine whether similar effects can be achieved as those seen in the premotor tDCS group.

Finally, the alpha ratio indexes from all tDCS groups in the pre-training session were found to significantly predict the improvement in FMA scores. First, alpha topography derived from the model could be treated as an indicator of potential

responders for future tDCS treatment or applications. This also suggests that the topography of alpha oscillatory activity may contain critical individual information relevant to the combination of tDCS and rehabilitation methods. More studies are needed to investigate the specificity of EEG topography in other tDCS protocols.

Our training protocol followed the recommendation of previous studies, but the post-treatment effects were similar across all three groups, with no additional effects detected in other domains. It is possible that our control group, which used an active control and employed a contemporary, evidence-based approach like mirror therapy, also provided an intensive and plausible treatment to improve motor function, resulting in comparable effects. However, there may be room to further optimize the current training program, such as adjusting the proportion of tDCS stimulation time and mirror therapy duration or increasing the functional components in the mirror therapy to augment the possible additive effects by tDCS.

The current study may be limited by the small sample size in each group, with one group not meeting the minimum requirement due to the impact of the pandemic. This could increase susceptibility to individual variability while reducing statistical sensitivity. Specifically, the absence of post-treatment tDCS effects on clinical outcomes might be partially due to the variability of individual characteristics, such as time since stroke, or insufficient sample size, which becomes non negligible in small sample sizes. Even though none of these characteristics differed between the three groups at baseline, they may still influence the effects of tDCS. Another limitation is the generalizability of the neural indexes to other tDCS combination protocols. The sensitivity of the neural indexes observed in our study was largely due to the connection between the PMC and MT, which does not guarantee effectiveness when combined with other neurorehabilitation methods.

V. Conclusion

The aim of the current study was to identify the optimal combination approach of MT and tDCS and explore potential therapeutic mechanisms by introducing the gating-by-inhibition model. This was the first study directly consider whether spatial pattern of EEG can gate alpha power during motor generation for better motor recovery. Our results demonstrated the superior effect of the PMC tDCS group on FMA-UE, particularly the retention effect over 3 months. Importantly, UE recovery was closely associated with cortical inhibition in the temporal area through high alpha power. Overall, tDCS appears to be an effective adjuvant to conventional rehabilitation techniques. However, to ensure its efficiency after treatment, the training program still needs further optimization, and patient baseline characteristics that might limit efficiency should be carefully considered as well. When applied with tDCS over the PMC with MT, although functional recovery was not immediately guaranteed, the benefits could be sustained up to 3 months and predicted by the spatial distribution of alpha power.

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