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Bilateral High-Definition Transcranial Direct Current Stimulation for Upper Extremity Rehabilitation in Stroke

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***Abstract*—Previous research shows that both anodal and cathodal high-definition transcranial direct current stimulation (HD-tDCS) may improve function of the upper extremity post stroke. However, most research has focused on the effects separately, therefore the purpose of this study was to determine the effects of performing simultaneous anodal-cathodal HD-tDCS. Five stroke participants received the stimulations in four visits with a two-week washout period: 1) anodal HD-tDCS to the ipsilesional primary motor cortex, 2) cathodal HD-tDCS to the contralesional dorsal premotor cortex, 3) bilateral anodal-cathodal HD-tDCS, and 4) sham. Active stimulation (anodal, cathodal, and bilateral) increased Fugl-Meyer upper extremity scores and decreased latency of ipsilesional M1-induced MEP. These results suggest that HD-tDCS could improve motor function of the upper extremity post-stroke, however, bilateral stimulation may not have an increased effect compared to anodal and cathodal HD-tDCS separately. This early phase study improves our understanding of neural circuitry and plasticity post stroke and HD-tDCS methods for improving function of the impaired arm post-stroke.**

Keywords— Stroke, high-definition transcranial direct current stimulation (HD-tDCS), bilateral stimulation, upper extremity rehabilitation.

I. Introduction

Stroke occurs when the blood supply to the brain is reduced or blocked completely, which prevents brain tissue from getting oxygen and nutrients [1]. More than 795,000 people in the United States experience a stroke each year. It is the fifth leading cause of death and the leading cause of serious long-term disability [2]. Specifically, a stroke that occurs in the motor and somatosensory cortices will cause focal damage to the cortices and to their descending pathways [3]. This causes a variety of physical effects, including hemiparesis, loss of sensation in the extremities, abnormal muscle synergies, spasticity, and loss of fine motor skills. [4]. Most (80%) ischemic stroke survivors report movement impairment on the side of the body contralateral to the lesioned hemisphere [4]. As a result of the damage to the ipsilesional motor cortex or its descending pathway, i.e., the corticospinal tract (CST) [5], there is a maladaptive hyperexcitability in the cortico-reticulospinal tract (CRST) in the contralesional hemisphere [5], hyperexcitability in post stroke motor impairments, specifically in more severe individuals and particularly in the expression of abnormal muscle synergies in the paretic upper limb [6]. The medial CRST primarily originates from the dorsal premotor cortex (PMd) and travels through the pontine reticular formation [7]. Previous studies applying transcranial magnetic stimulation (TMS) to patients after stroke demonstrated that the medial CRST is responsive to the excitatory ipsilateral input from the PMd in the contralesional hemisphere [8, 9]. This finding makes the contralesional PMd a potential target for combating moderate-to-severe movement impairment.

Transcranial direct current stimulation (tDCS) has been shown to quickly and safely modulate cortical excitability [10]. However, the effect of conventional tDCS is limited as it uses large size "sponge" electrodes, making it difficult to target a specific region of interest in the brain. To address this limitation, this study used a TMS verified neural navigated targeted high-definition tDCS (HD-tDCS). HD-tDCS has been shown to be able to modulate a specific area of the brain and

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rebalance interhemispheric cortical activity [11]. Previous studies have found that both anodal and cathodal HD-tDCS can be effective at improving post stroke motor function [12]. However, to the best of our knowledge, these have only been evaluated separately. Therefore, the overall objective of this proof-of-concept study is to explore the potential of simultaneous anodal-cathodal targeted HD-tDCS to modulate the excitability of specific cortical motor regions and their pathways to improve post-stroke upper extremity impairments. Our hypotheses are that 1) facilitating the ipsilesional primary motor cortex (M1) improves the excitability of the damaged CST, thus, reducing the CRST hyperexcitability and motor impairments, 2) inhibiting the contralesional dorsal premotor cortex (cPMd) directly reduces the CRST hyperexcitability and thus, may also improve motor behaviors and 3) bilateral stimulation will both facilitate and inhibit simultaneously and have a greater effect than performing anodal or cathodal separately.

II. Methods

Five participants (2 female) with stroke in the chronic phase (> 7 months) consented for the study (IRB # 14906). The demographics of participants are provided in **Table 1**.

TABLE I. Stroke Participant Demographics

Subject ID	Lesion Side	Sex	Age	Time post stroke	FM-UE (Total: 66)
S1	R	M	73	25 months	10
S2	L	M	44	7 months	43
S3	L	M	70	41 months	12
S4	L	F	67	95 months	19
S5	R	F	57	8 months	18

Prior to HD-tDCS stimulation, the participants were screened at baseline using the Fugl-Meyer upper extremity (FM-UE) score [13] and transcranial magnetic stimulation (TMS)-induced motor evoked potentials (MEP). The TMS-induced MEP were assessed to determine the use of the ipsilesional corticospinal tract and the contralesional cortico-reticulospinal tract [8, 9]. The paired-pulse TMS (Magstim® BiStim^2, The Magstim Company Ltd., Spring Gardens, Whitland, UK) was applied at the respective hotspots for the Biceps Brachii, over the ipsilesional primary motor cortex (from which the corticospinal tract originates) and contralesional dorsal premotor cortex (from which the cortico-reticulospinal tract originates) with reference to the paretic arm, using a figure-eight coil [8]. We used the paired-pulse TMS with a conditioning pulse (65% stimulator maximum intensity) followed by a testing pulse (85% stimulator maximum intensity), to avoid the need to pre-activate the muscle (which could cause the bias of background EMG) [14], with paired-pulse intervals of 25 ms [8]. The center of the coil was positioned tangentially to the skull with the handle at 45° from the parasagittal plane: posterior-anterior orientation for ipsilesional M1 and anterior-posterior orientation for contralesional PMd [15, 16]. The M1 hotspot is defined as the grid-point that results in the largest response in the target muscle, and was found for the ipsilesional M1 and contralesional M1 hemisphere through stimulation of a 5 x 5 grid of 1 cm spaced sites on the scalp over motor areas of each hemisphere (centered at C3/4 of 10-20 EEG system) [17]. The "hot-spot" of the contralesional PMd was identified using a reference point of 1 cm medial and 2.5 cm anterior of the M1 "hot-spot" at the contralesional hemisphere [15, 18]. We determined MEP status using criteria previously reported [19]: the patient was considered MEP+ if MEPs of any amplitude are observed at a consistent latency on at least 5 out 10 trials; otherwise, MEP– . After determining the status of MEP, at least eight more pulses (inter-stimulus interval: 2-3s) were applied to the identified hotspot to get a robust estimate of the latency of the MEP. Together with determination trials, we calculated average latency across all positive trials (more than 18 trials if MEP+) to determine the latency and amplitude of MEP.

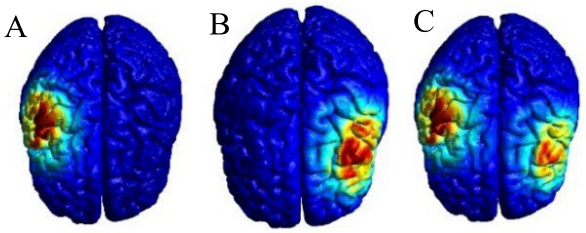

Fig. 1. Electrical field estimation **of** (A) Anodal HD-DCS, (B) Cathodal tDCS, (C) Bilateral Anodal-Cathodal HD-tDCS

After the baseline assessment, the participants continued to participate in a randomized, double-blind (Participant, Outcomes Assessor) cross-over pilot study with four visits: 1) anodal high-definition transcranial direct stimulation (HD-tDCS) over the ipsilesional M1, 2) cathodal HD-tDCS over contralesional PMd, 3) bilateral anodal-cathodal HD-tDCS and 4) sham stimulation, with a two-week washout period in-between. The order of the stimulations was computer randomized.

The HD-tDCS method used two Soterix Medical HD-tDCS units (4x1 HD-tDCS unit, Soterix Medical Inc, Woodbridge, New Jersey, USA). Each unit consisted of five small (1 centimeter in diameter) electrodes with the main stimulation electrode in the center, and four surrounding co-centric electrodes with opposite polarity. The HD-tDCS electrodes were mounted onto a standard 10-20 EEG cap. The stimulation dosage was set as 2 mA, for 20 min, the optimal safe dosage to influence neuroplasticity according to the safety guidelines of HD-tDCS [20, 21]. During active anodal and cathodal visits, the opposing side was set to sham. For sham stimulation, the HD-tDCS unit was set to the automatic sham feature, which produces a sham waveform based on the

indicated "real" waveform by only ramping the current to 2mA at the start and end of the stimulation to provide the same feeling as active stimulation to the participants. During the sham visit both units were set to sham. The stimulation location was identified using subject-specific 1.5T MR images (the T1 weighted images were obtained by using a T1 SAG FLAIR sequence with FOV = 22 cm, Slice Thickness: 5 mm and the T2 weighted images were obtained by suing T2 AX sequence with the same FOV and Slide Thickness values as the T1) and verified by the TMS-induced MEP as explained, with the center electrode on the TMS "hot-spot" and 40-45 mm (depending on the size of the head) distance between the center and surrounding electrodes [8, 19]. This is the optimal distance based on our previous simulation study [23]. Electrical fields in the brain were created in SimNIBS v4.0b to confirm that the targeted brain area was stimulated and that bilateral stimulation was not crossing over and merging together (as illustrated in **Fig. 1**) [24]. The effect of HD-tDCS was determined by the change in FM-UE scores and the change of MEP latencies.

III. Results

The computer randomized order that the participants received the treatment is shown in **Table II.** FM-UE (scored 0-66) increased in all five participants after active stimulation (anodal, cathodal, or bilateral). Anodal stimulation yielded the largest difference in all participants except subject 4 (S4). S4 was observed to have larger improvement with both cathodal and bilateral, additionally was the only participant to have the biggest increase with bilateral stimulation. **Fig. 2** displays the individual results of the FM-UE assessment.

TABLE II. Stroke Participant Stimualtion Order

Subject ID	Visit 1	Visit 2	Visit 3	Visit 4
S1	Cathodal	Sham	Anodal	Bilateral
S2	Cathodal	Sham	Anodal	Bilateral
S3	Bilateral	Anodal	Cathodal	Sham
S4	Bilateral	Cathodal	Anodal	Sham
S5	Bilateral	Sham	Cathodal	Anodal

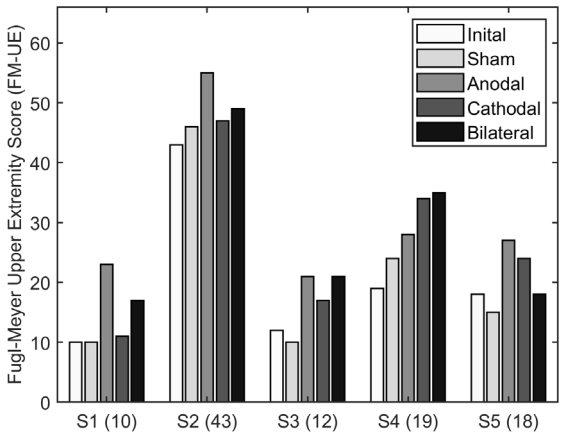

Fig. 2. Fugl-Meyer Upper Extremity (FM-UE) scores per participant before and after stimulation. Initial FM-UE are displayed in parentheses after subject number.

The ipsilesional M1-induced MEP of the impaired side was detected at the baseline for all five participants. Latency of ipsilesional M1 MEP decreased in all participants after active stimulation (anodal, cathodal, and bilateral). The largest difference was observed in subject 1 (S1) who had the lowest initial FM-UE score. The smallest difference was observed in subject 2 (S2) who had the highest initial FM-UE score **(Fig. 3)**. The contralesional PMd-induced MEP was either delayed or disappeared after active stimulation in each instance with exception of subject 5 (S5) bilateral (**Table III**).

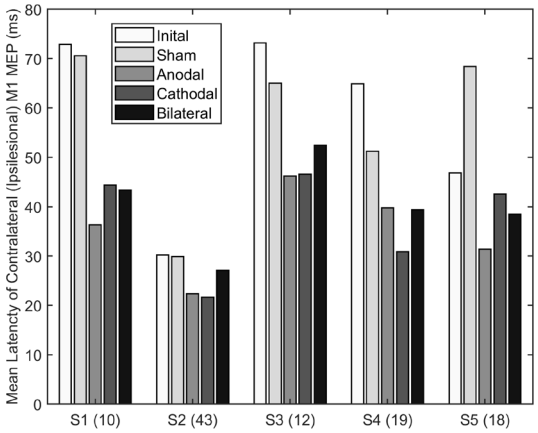

Fig. 3. Latency of Contralateral to impaired side (ipsilesional) per participant before and after stimulation. Initial FM-UE are displayed in parentheses after subject number.

TABLE III. Mean Latency of Ipsilateral (Contralesional) PMd MEP (ms)

Subject ID	Initial	Sham	Anodal	Cathodal	Bilateral
S1	91.2 ms	97.7 ms	102.7 ms	MEP -	MEP -
S2	73.1 ms	73.9 ms	MEP -	MEP -	104.5 ms
S3	79.4 ms	79.7 ms	82.8 ms	MEP-	94.0 ms
S4	76.8 ms	71.8 ms	80.9 ms	MEP-	94.5 ms
S5	68.3 ms	66.0 ms	78.4 ms	97.6 ms	63.6 ms

IV. Discussion

This study provides support of the use of both targeted M1 anodal and PMd cathodal HD-tDCS as a method for stroke rehabilitation. We observed that facilitating ipsilesional M1 using anodal stimulation or inhibiting PMd using cathodal stimulation improved FM-UE scores and decreased the latency of ipsilesional M1 TMS-induced MEP. As the minimally clinically important difference for the FM-UE ranges from 4.25-7.25 points [25].This improvement is consistent with prior studies on the use HD-tDCS post stroke [26]. In addition, both anodal and cathodal HD-tDCS either delayed or

disappeared the PMd-induced contralesional MEP. These findings strengthen existing knowledge that M1 anodal stimulation may improve the excitability of the damaged CST and improve motor impairments. More importantly, the facilitation of the CST may also reduce hyperexcitability in the CRST. This is likely because the increased cortical excitability of ipsilesional M1 may enhance the super bulbar inhibition to the reticulospinal tract via the cortico-reticular pathways [7]. Further, inhibiting at PMd may directly reduce CRST excitability. This finding is significant as maladaptive CRST recruitment is known as the key drive of post-stroke spasticity [5].

While bilateral stimulation did improve both FM-UE scores and decrease the latency of M1-induced ipsilesional MEP, it did not appear to have a superior effect compared to anodal stimulation and performed similarly to cathodal. Previous studies using conventional tDCS utilizing bilateral stimulation (anodal stimulation over the affected hemisphere and cathodal over the contralesional hemisphere) have had varied results on the effectiveness of bilateral compared to anodal and cathodal separately [26]. It could be that despite the modeling results of simultaneous anodal-cathodal HD-tDCS, the anodal and cathodal electric fields are crossing the hemisphere and thus not enhancing the effects. However, conclusions of bilateral stimulation are difficult to make with our limited sample size (n=5).

Overall, this study improves our understanding of neural circuitry and plasticity post stroke. It shows the benefit of neuro-navigation HD-tDCS and provides preliminary insight into bilateral HD-tDCS stimulation. Future work is required by increasing sample size and performing additional modeling on bilateral tDCS [27]. Furthermore, we will also explore other stimulation modalities such as transcranial alternating current stimulation (tACS) [28] to modulate the brain network via oscillatory coupling between the stimulation and sensorimotor rhythms.

REFERENCES

[1] What is a Stroke. 2022 March 21 2022]; Available from: https://www.nhlbi.nih.gov/health/stroke.

[2] Virani, S.S., et al., Heart disease and stroke statistics—2020 update: a report from the American Heart Association. Circulation, 2020. 141(9): p. e139-e596.

[3] Nudo, R.J., et al., Neural substrates for the effects of rehabilitative training on motor recovery after ischemic infarct. Science, 1996. 272(5269): p. 1791-1794.

[4] Parker, V.M., D.T. Wade, and R. Langton Hewer, Loss of arm function after stroke: measurement, frequency, and recovery. Int Rehabil Med, 1986. 8(2): p. 69-73.

[5] Li, S., et al., A Unifying Pathophysiological Account for Post-stroke Spasticity and Disordered Motor Control. Front Neurol, 2019. 10: p. 468.

[6] Tian R, Dewald J.P.A. Yang Y, Assessing the Usage of Indirect Motor Pathways following a Hemiparetic Stroke, IEEE Trans Neural Syst Rehabilitation Eng, vol 29, pp. 1568-1572, Aug. 2021.

[7] Jang, S.H. and S.J. Lee, Corticoreticular tract in the human brain: a mini review. Frontiers in Neurology, 2019. 10: p. 1188.

[8] Schwerin, S.C., J. Yao, and J.P. Dewald, Using paired pulse TMS to facilitate contralateral and ipsilateral MEPs in upper extremity muscles of chronic hemiparetic stroke patients. Journal of Neuroscience Methods, 2011. 195(2): p. 151-160.

[9] Bestmann, S., et al., The role of contralesional dorsal premotor cortex after stroke as studied with concurrent TMS-fMRI. Journal of Neuroscience, 2010. 30(36): p. 11926-11937.

[10] Orrù, G., et al., Motor stroke recovery after tDCS: a systematic review. Reviews in the Neurosciences, 2020. 31(2): p. 201-218.

[11] Kim, H., et al., Task-Related Hemodynamic Changes Induced by High-Definition Transcranial Direct Current Stimulation in Chronic Stroke Patients: An Uncontrolled Pilot fNIRS Study. Brain Sciences, 2022. 12(4): p. 453.

[12] Bao, S.C., et al., Cortico-Muscular Coherence Modulated by High-Definition Transcranial Direct Current Stimulation in People With Chronic Stroke. IEEE Transactions on Neural Systems and Rehabilitation Engineering, 2019. 27(2): p. 304-313.

[13] Huang, Y.-J., et al., High-Definition Transcranial Direct Current with Electrical Theta Burst on Post-Stroke Motor Rehabilitation: A Pilot Randomized Controlled Trial. Neurorehabilitation and Neural Repair, 2022. 36(9): p. 645-654.

[14] Williamson, J.N., et al., High-Definition Transcranial Direct Current Stimulation for Upper Extremity Rehabilitation in Moderate-to-Severe Ischemic Stroke-A Pilot Study. Frontiers in Human Neuroscience. 2023, 17: p. 1286238.

[15] Gladstone, D.J., C.J. Danells, and S.E. Black, The Fugl-Meyer Assessment of Motor Recovery after Stroke: A Critical Review of Its Measurement Properties. Neurorehabilitation and Neural Repair, 2002. 16(3): p. 232-240.

[16] Oliveri, M., et al., Paired transcranial magnetic stimulation protocols reveal a pattern of inhibition and facilitation in the human parietal cortex. The Journal of physiology, 2000. 529(2): p. 461-468.

[17] Tscherpel, C., et al., The differential roles of contralesional frontoparietal areas in cortical reorganization after stroke. Brain stimulation, 2020. 13(3): p. 614-624.

[18] Tscherpel, C., et al., Age affects the contribution of ipsilateral brain regions to movement kinematics. Human brain mapping, 2020. 41(3): p. 640-655.

[19] Schwerin, S., et al., Ipsilateral versus contralateral cortical motor projections to a shoulder adductor in chronic hemiparetic stroke: implications for the expression of arm synergies. Exp Brain Res, 2008. 185(3): p. 509-19.

[20] Stephan, M.A., et al., Melodic priming of motor sequence performance: The role of the dorsal premotor cortex. Frontiers in Neuroscience, 2016. 10: p. 210.

[21] Stinear CM, B.W., Ackerley SJ, Smith MC, Borges VM, Barber PA. , PREP2: A biomarker-based algorithm for predicting upper limb function after stroke. Annals of Clinical Translational Neurology, 2017. 4(11): p. 811-820.

[22] Mackenbach, C., R. Tian, and Y. Yang. Effects of electrode configurations and injected current intensity on the electrical field of transcranial direct current stimulation: A simulation study. in 2020 42nd Annual International Conference of the IEEE Engineering in Medicine & Biology Society (EMBC). 2020. IEEE.

[23] Thielscher, A., A. Antunes, and G.B. Saturnino. Field modeling for transcranial magnetic stimulation: A useful tool to understand the physiological effects of TMS? in 2015 37th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC). 2015.

[24] Hiragami, S., Y. Inoue, and K. Harada, Minimal clinically important difference for the Fugl-Meyer assessment of the upper extremity in convalescent stroke patients with moderate to severe hemiparesis. Journal of physical therapy science, 2019. 31(11): p. 917-921.

[25] Bao, S.C., et al., Cortico-Muscular Coherence Modulated by High-Definition Transcranial Direct Current Stimulation in People With Chronic Stroke. IEEE Trans Neural Syst Rehabil Eng, 2019. 27(2): p. 304-313.

[26] Di Lazzaro, V., et al., Immediate and Late Modulation of Interhemipheric Imbalance With Bilateral Transcranial Direct Current Stimulation in Acute Stroke. Brain Stimulation, 2014. 7(6): p. 841-848.

[27] Peng R H-T; He D, James, S.A., Williamson, J.N., Skadden C; Jain S, Hassaneen W, Miranpuri A, Kaur A, Sarol J. N, Yang Y, Trials, 2024; 25:p. 34.

[28] Mulyana, Beni and Tsuchiyagaito, Aki and Smith, Jared, et. al. Online closed-loop real-time tES-fMRI for brain modulation: A technical report. Brain and Behavior, 2022;12:p.e2667.