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Transcranial Direct Current Stimulation Facilitates Motor Learning Post Stroke: A Systematic Review and Meta-Analysis

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ABSTRACT

Background. Transcranial direct current stimulation (tDCS) is an attractive protocol for stroke motor recovery. The current systematic review and meta-analysis investigated the effects of tDCS on motor learning post stroke; motor improvements from baseline to long-term retention.

Methods. Seventeen studies reported long-term retention testing (retention interval: minimum 6 days – maximum 24 weeks) and qualified for our meta-analysis. Motor outcome measures included: (a) three motor function tests (i.e., Fugl-Meyer Assessment, National Institute of Health Stroke Scale, and Berg Balance Scale), (b) Purdue Pegboard Test, and (c) motor skill acquisition tests.

Results. A random effects model meta-analysis showed a significant overall effect size (standardized mean difference = 0.61; $p < 0.0001$; low heterogeneity, $I^2 = 13.15\%$; and high classic fail-safe $N = 163$). Moderator variable analyses revealed beneficial effects of tDCS on motor learning: (a) stimulation protocols: anodal on ipsilesional hemisphere, cathodal on contralesional hemisphere, or bilateral; (b) recovery stage: chronic stroke; and (c) stimulation timing: tDCS before or during motor training.

Conclusion. Our meta-analysis revealed robust benefits of active tDCS on permanent motor learning effects post stroke.

INTRODUCTION

Stroke is a leading cause of chronic motor disabilities in the United States, and astoundingly the frequency of occurrence is nearly 800,000 per year.[1] Moreover, 80% of chronic stroke patients have motor deficits in both the ipsilesional and contralesional limbs. Unfortunately, rehabilitation programs have not solved the issues of motor impairments and long-term hemiparesis.[1 2] Thus, stroke researchers and rehabilitation specialists are continually searching for more effective treatment.

Recently, a popular stroke treatment protocol involves transcranial direct current stimulation (tDCS), a non-invasive brain stimulation (NIBS) technique. tDCS is an economical, portable, and easily accessible protocol for neurorehabilitation.[3] The tDCS technique provides two weak (e.g., 1−2 mA) electrical stimulations to the scalp by surface electrodes: (a) anodal stimulation and (b) cathodal stimulation. A long history of tDCS studies reported that anodal stimulation typically increases cortical excitability whereas cathodal stimulation decreases cortical excitability in an animal model[4 5] and in humans.[6 7] Liebetanz and colleagues posited that the polarity-specific modulation of human motor cortex excitability following tDCS is attributed to small alterations in resting membrane potentials.[8] A common mechanism underlying stroke motor recovery post tDCS involves the interhemispheric competition model.[9 10] Typically, the post stroke magnitude of interhemispheric inhibition from the contralesional hemisphere is greater than the ipsilesional hemisphere. Inhibition from the contralesional hemisphere interferes with the level of cortical excitability in the ipsilesional hemisphere, thus, resulting in a more impaired paretic limb. This theory assumes that balancing both excitatory and inhibitory activation between hemispheres after tDCS protocols (i.e., anodal stimulation on ipsilesional

hemisphere; cathodal stimulation on contralesional hemisphere; bilateral stimulation on both hemispheres) facilitates functional recovery in stroke survivors.

Earlier narrative reviews reported beneficial effects of tDCS on stroke motor functions (e.g., greater Fugl-Meyer Assessment score or walking ability).[3 11-14] Despite the presumed evidence that tDCS transiently improves motor performance post stroke,[13] whether long-term improvements in motor functions are permanent is unclear. The classic definition of motor learning as a set of internal processes facilitated by experience or practice leading to relatively permanent changes in the capabilities to produce behavioral actions includes two distinct phases: (a) acquisition and (b) retention (or transfer).[15-17] The motor acquisition phase involves temporary changes in behavior after practice (i.e., motor performance) whereas retention or transfer represents relatively permanent changes in behavior. Relatively permanent behavioral changes are measured by comparing baseline motor performances with long-term retention testing or transfer tasks.[16 18] Frequently, rehabilitation programs only involve measuring transient movement changes activated during a short acquisition phase rather than permanent motor action changes. Therefore, our systematic review and meta-analysis compared studies that investigated the effects of tDCS on long-term motor learning post stroke.

Several systematic reviews revealed motor learning evidence in stroke survivors after tDCS interventions.[13 14 19 20] Although two review studies found long-term motor improvements post tDCS protocols, these findings were not based on the meta-analytic technique.[13 19] Two other meta-analyses revealed long-term improvement in activities of daily living[20] as well as clinical assessments[14] after tDCS interventions. However, these meta-analytic findings were based on only two or three studies. Moreover, recent studies reported greater motor learning effects after tDCS protocols combined with a behavioral therapy than only tDCS protocols.[21 22]

Systematically reviewing and conducting a meta-analysis on studies that used tDCS protocols coupled with motor interventions will advance our understanding of long-term motor learning effects post stroke. Thus, the current stroke meta-analysis is unique in two aspects: (a) relatively permanent motor learning effects (long-term) of active tDCS combined with motor training in comparison to sham tDCS with motor training and (b) substantially more studies (N = 17) were identified and submitted to the meta-analysis than previous reviews. Further, we asked three leading questions: (a) Do tDCS protocols, anodal stimulation on ipsilesional hemisphere, cathodal stimulation on contralesional hemisphere, or bilateral stimulation improve motor learning post stroke? (b) Are relatively permanent behavioral effects of tDCS interventions found in each stage of stroke recovery (i.e., acute, sub-acute, and chronic)? and (c) Does timing of tDCS intervention (i.e., before versus during motor training) influence long-term motor learning in stroke survivors?

METHODS

Literature search and study selection

Our literature search concentrated on tDCS studies (2005 − 2015) that investigated long-term effects on motor functions post stroke. An initial search included PubMed, ISI's Web of Knowledge, and Cochrane Database of Systematic Reviews. Seven keywords were: (a) stroke, (b) cerebrovascular accident, (c) brain infarct, (d) transcranial direct current stimulation (tDCS), (e) motor learning, (f) long-term retention test (delayed), and (g) transfer task. We initially identified 53 potential research studies.

Inclusion criteria for our meta-analysis were: (a) quantitative evaluation of tDCS effects on motor learning post stroke, (b) a retention interval at least 5 days post intervention, (c) tDCS stimulation (e.g., anodal, cathodal, or bilateral stimulations) comparing pre and post treatment, (d)

active stimulation versus sham control comparison, and (e) tDCS combined with motor training (e.g., stimulation before motor training or stimulation during motor training). Following these criteria, 36 studies were excluded: (a) 12 review articles, (b) 15 studies with no retention testing, (c) one short retention interval, (d) four case studies: single participant or no statistical analyses, (e) three studies using tDCS protocols only, and (f) one study that did not include a tDCS sham control group. The remaining 17 studies qualified for inclusion in our meta-analysis.[21-37]

Fifteen studies compared active stimulation with sham control groups and two studies used pre versus post intervention comparisons. Stimulation protocols were categorized with (a) anodal stimulation on M1 of ipsilesional hemisphere (seven studies), (b) cathodal stimulation on M1 of contralesional hemisphere (five studies), and (c) bilateral (anodal + cathodal) stimulation (five studies). Studies for the three recovery stages post stroke included: (a) acute (1 day – 1 month; two studies), (b) sub-acute (1 month – 6 months; four studies), and (c) chronic (greater than 6 months; 11 studies).[38] Two stimulation protocols varied by onset in relation to motor training: (a) stimulation before motor training (seven studies) and (b) stimulation during motor training (10 studies). Table 1 displays the characteristics of the 17 comparisons we included in this meta-analysis.

Table 1. Characteristics of each comparison included in the present meta-analysis (studies listed alphabetically)

Study	Total N	Age (yrs.)	Gender	Rx Onset Post Stroke (month)	Stroke Type	Affected Hemisphere	Initial Impairment	Recovery Stage
Bolognini *et al*[21]	14	46.7	9 F, 5 M	35.2	12 I, 2 H	8 L, 6 R	26.0 / 66 (FMA)	chronic
Celnik *et al*[23]	9	55.3	4 F, 5 M	55.7	9 I	5 L, 4 R	94.0 / 100 (%FMA)	chronic
Danzl *et al*[24]	8	67.8	4 F, 4 M	48.0	6 I, 2 H	8 L	32.4 / 56 (BBS)	chronic
Fusco *et al*[25]	11	58.4	6 F, 5 M	1.0	11 I	6 L, 5 R	24.7 / 66 (FMA)	sub-acute
Geroin *et al*[26]	30	62.7	7 F, 23 M	26.4	30 I	N/A	79.9 / 100 (ESS)	chronic
Hesse *et al*[22]	96	65.0	37 F, 59 M	1.0	96 I	51 L, 45 R	8.0 / 66 (FMA)	sub-acute
Khedr *et al*[27]	40	58.3	14 F, 26 M	1.0	40 I	18 L, 22 R	10.7 / 42 (NIHSS)	sub-acute
Kim *et al*[28]	18	57.8	5 F, 13 M	1.0	18 I	9 L, 9 R	37.2 / 66 (FMA)	sub-acute
Lazzaro *et al*[29]	20	64.8	7 F, 13 M	0.1	20 I	12 L, 8 R	5.9 / 42 (NIHSS)	acute
Lefebvre *et al*[30]	18	61.0	6 F, 12 M	31.2	16 I, 2 H	8 L, 10 R	7.1 / 25 (PPT)	chronic
Lefebvre *et al*[31]	19	65.0	3 F, 16 M	62.4	N/A	14 L, 5 R	7.4 / 25 (PPT)	chronic
Lindenberg *et al*[32]	20	58.8	5 F, 15 M	35.4	20 I	13 L, 7 R	39.0 / 66 (FMA)	chronic
Nair *et al*[33]	14	55.8	5 F, 9 M	30.5	14 I	8 L, 6 R	30.5 / 66 (FMA)	chronic
Sattler *et al*[37]	20	65.2	6 F, 14 M	0.2	20 I	N/A	48.0 / 66 (FMA)	acute
Takeuchi *et al*[34]	27	61.5	10 F, 17 M	67.1	N/A	14 L, 13 R	78.6 / 100 (%FMA)	chronic
Wu *et al*[35]	90	47.6	21 F, 69 M	6.0	53 I, 37 H	43 L, 47 R	10.0 / 66 (FMA)	chronic
Zimerman *et al*[36]	12	58.3	6 F, 6 M	30.0	12 I	5 L, 7 R	64.0 / 66 (FMA)	chronic

Abbreviation. BBS: Berg Balance Scale; ESS: European Stroke Scale; F: female; FMA: Fugl-Meyer Assessment; H: hemorrhagic; I: ischemic; L: left; M: male; NIHSS: National Institutes of Health Stroke Scale; PPT: Purdue Pegboard Test; R: right, Rx: treatment

Motor outcome measures

Quantifying the effects of tDCS on motor learning and long-term retention involved motor function tests, Purdue Pegboard Test, and motor skill acquisition tests. Eleven studies reported motor function tests: (a) Fugl-Meyer Assessment (upper limb motor function; higher score indicates motor improvement), (b) Berg Balance Scale (static balance function; higher score shows low fall risk), and (c) National Institute of Health Stroke Scale (overall stroke impairment; lower score reveals better recovery post stroke). Two studies used the Purdue Pegboard Test (manual dexterity; higher score means better dexterity) and four studies reported a broad set of action tests as motor skill acquisition: (a) sequencing task (sequential pressing of a 5-element sequence on a 4-button electronic keyboard with paretic hand), (b) key pressing task (number of correct key presses with 2 – 5th digit of paretic fingers over 30 seconds), (c) 6 minute walking test (distance with maximum walking speed for 6 minutes), and (d) pinch force task (maximum pinch force with paretic thumb and index fingers). Each study contributed data from one primary motor outcome measure. This conventional procedure minimizes data biasing effects.[39 40]

Data synthesis and analysis

Four tables display specific details for each of the 17 studies. Tables 1 and 2 summarize relevant characteristics and tDCS rehabilitation protocols. Table 3 provides tDCS parameters and Table 4 displays summary statistics, outcome measures, individual weighted effect sizes, calculated overall effect size, Q statistic, I^2, T^2, and fail-safe N. According to Borenstein and colleagues,[41] a random effects model is appropriate when effect sizes between studies are posited as different. Thus, we used a random effect model for calculating the overall effect size and individual effect sizes for each subgroup.

Table 2. tDCS rehabilitation protocols

Study	Limb	Treatment	Session	Stimulation
Bolognini *et al*[21]	upper	tDCS during CIMT	10 sessions	atDCS on iH + ctDCS on cH; sham
Celnik *et al*[23]	upper	PNS + tDCS before motor practice	1 session	PNS + atDCS on iH; PNS + sham
Danzl *et al*[24]	lower	tDCS before RGO training	12 sessions (3 times per week)	atDCS on iH, sham
Fusco *et al*[25]	upper	tDCS before motor training	10 sessions (5 times per week)	ctDCS on cH, sham
Geroin *et al*[26]	lower	tDCS during robot-assist gait training	10 sessions (5 times per week)	atDCS on iH, sham
Hesse *et al*[22]	upper	tDCS during arm robot training	30 sessions (5 times per week)	atDCS on iH, ctDCS on cH, sham
Khedr *et al*[27]	upper	tDCS before motor training	6 daily consecutive sessions	atDCS on iH, ctDCS on cH, sham
Kim *et al*[28]	upper	tDCS during OT	10 sessions (5 times per week)	atDCS on iH, ctDCS on cH, sham
Lazzaro *et al*[29]	upper	tDCS during CIMT	5 daily consecutive sessions	atDCS on iH + ctDCS on cH, sham
Lefebvre *et al*[30]	upper	tDCS during motor skill learning task	1 session	atDCS on iH + ctDCS on cH, sham
Lefebvre *et al*[31]	upper	tDCS during motor skill learning task	1 session	atDCS on iH + ctDCS on cH, sham
Lindenberg *et al*[32]	upper	tDCS during PT + OT	5 daily consecutive sessions	atDCS on iH + ctDCS on cH, sham
Nair *et al*[33]	upper	tDCS during OT	5 daily consecutive sessions	ctDCS on cH, sham
Sattler *et al*[37]	upper	repetitive PNS + tDCS before OT	5 daily consecutive sessions	atDCS on iH, sham
Takeuchi *et al*[34]	upper	tDCS + rTMS before motor training	1 session	atDCS on iH, sham
Wu *et al*[35]	upper	tDCS before PT	20 sessions (5 times per week)	ctDCS on cH, sham
Zimerman *et al*[36]	upper	tDCS during motor sequence task	1 session	ctDCS on cH, sham

Abbreviations. atDCS: anodal transcranial direct current stimulation; cH: contralesional hemisphere; CIMT: constraint-induced movement therapy; ctDCS: cathodal transcranial direct current stimulation; iH: ipsilesional hemisphere; OT: occupational therapy; PNS: peripheral nerve stimulation; PT: physical therapy; RGO: robotic gait orthosis; rTMS: repetitive transcranial magnetic stimulation

Table 3. tDCS parameters

Study	Stimulation	Reference electrode	Site	Intensity (mA)	Size	Duration (min)
Bolognini *et al*[21]	Bi	N/A	M1	2	35 cm^2	40
Celnik *et al*[23]	Uni-A	contralateral supraorbital region	M1	1	7.6 × 7.6 cm	20
Danzl *et al*[24]	Uni-A	contralateral supraorbital region	M1 (Leg area)	2	25 cm^2	20
Fusco *et al*[25]	Uni-C	contralateral shoulder	M1	1.5	35 cm^2	10
Geroin *et al*[26]	Uni-A	contralateral supraorbital region	M1 (Leg area)	1.5	35 cm^2	7
Hesse *et al*[22]	Uni-A	contralateral supraorbital region	M1	2	35 cm^2	20
Khedr *et al*[27]	Uni-A	contralateral supraorbital region	M1	2	5 × 7 cm	25
Kim *et al*[28]	Uni-C	contralateral supraorbital region	M1	2	25 cm^2	20
Lazzaro *et al*[29]	Bi	N/A	M1	2	35 cm^2	40
Lefebvre *et al*[30]	Bi	N/A	M1	1	35 cm^2	30
Lefebvre *et al*[31]	Bi	N/A	M1	1	35 cm^2	30
Lindenberg *et al*[32]	Bi	N/A	M1	1.5	16.3 cm^2	30
Nair *et al*[33]	Uni-C	contralateral supraorbital region	M1	1	N/A	30
Sattler *et al*[37]	Uni-A	N/A	M1	1.2	35 cm^2	13
Takeuchi *et al*[34]	Uni-A	contralateral supraorbital region	M1 (FDI)	1	25 cm^2	20
Wu *et al*[35]	Uni-C	contralateral shoulder	M1	1.2	4.5 × 5.5 cm	20
Zimerman *et al*[36]	Uni-C	contralateral supraorbital region	M1	1	25 cm^2	20

Abbreviations. Bi: bilateral; FDI: first dorsal interosseous; M1: primary motor cortex; Uni-A: unilateral-anodal; Uni-C: unilateral-cathodal

Table 4. Summary statistics for the 17 comparisons in this meta-analysis

Study	Retention Period	Outcome Measure	Rx / Control (N)	SMD	95% CI		Relative Weight
Bolognini *et al*[21]	4 weeks	FMA (Bi tDCS during CIMT at retention: Rx vs. baseline: Control)	7	1.40	0.36	2.44	3.0
Celnik *et al*[23]	6 days	Mean number of correct key press (PNS + atDCS on iH before motor practice at retention: Rx vs. PNS + sham before motor practice at retention: Control)	9 / 9	0.62	-0.09	1.33	6.3
Danzl *et al*[24]	4 weeks	BBS change (atDCS on iH before RGO training at retention: Rx vs. sham before RGO training at retention: Control)	4 / 4	0.07	-1.31	1.46	1.7
Fusco *et al*[25]	4 weeks	FMA (ctDCS on cH before motor training at retention: Rx vs. sham before motor training at retention: Control)	5 / 6	0.29	-0.90	1.48	2.3
Geroin *et al*[26]	2 weeks	Six minute walking test (m) (atDCS on iH during robot-assist gait training at retention: Rx vs. sham during robot-assist gait training at retention: Control)	10 / 10	0.38	-0.50	1.27	4.1
Hesse *et al*[22]	12 weeks	FMA (atDCS on iH during arm robot training at retention: Rx vs. sham during arm robot training at retention: Control)	28 / 28	0.04	-0.48	0.56	11.8
Khedr *et al*[27]	12 weeks	NIHSS (atDCS on iH before motor training at retention: Rx vs. sham before motor training at retention: Control)	14 / 13	1.59	0.73	2.46	4.3
Kim *et al*[28]	24 weeks	FMA (ctDCS on cH during OT at retention: Rx vs. sham during OT at retention: Control)	5 / 7	1.30	0.04	2.57	2.0

Lazzaro *et al*[29]	12 weeks	NIHSS (atDCS on iH + ctDCS on cH during CIMT at retention: Rx vs. sham during CIMT at retention: Control)	10 / 10	0.36	-0.52	1.24	4.1
Lefebvre *et al*[30]	1 week	PPT (atDCS on iH + ctDCS on cH during motor skill learning task at retention: Rx vs. baseline: Control)	18	0.60	0.10	1.10	12.8
Lefebvre *et al*[31]	1 week	PPT (atDCS on iH + ctDCS on cH during motor skill learning task at retention: Rx vs. sham during motor skill learning task at retention: Control)	19 / 19	0.87	0.35	1.40	11.6
Lindenberg *et al*[32]	1 week	FMA (atDCS on iH + ctDCS on cH during PT + OT at retention: Rx vs. sham during PT + OT at retention: Control)	10 / 10	0.29	-0.59	1.17	4.2
Nair *et al*[33]	1 week	FMA (ctDCS on cH during OT at retention: Rx vs. sham during OT at retention: Control)	7 / 7	1.16	0.03	2.30	2.5
Sattler *et al*[37]	4 weeks	FMA (repetitive PNS + atDCS on iH before OT at retention: Rx vs. repetitive PNS + sham before OT at retention: Control)	10 / 10	0.07	-0.81	0.95	4.2
Takeuchi *et al*[34]	1 week	Pinch force of paretic hand (% of Pre-stimulation) (atDCS on iH + 1 Hz rTMS on cH before motor training at retention: Rx vs. sham on iH + 1 Hz rTMS on cH before motor training at retention: Control)	9 / 9	0.51	-0.42	1.45	3.7
Wu *et al*[35]	4 weeks	FMA (ctDCS on cH before PT at retention: Rx vs. sham before PT at retention: Control)	45 / 45	0.72	0.29	1.14	17.8

Zimerman *et al*[36]	12 weeks	Number of correct sequence (ctDCS on cH during motor sequence task at retention: Rx vs. sham during motor sequence task at retention: Control)	5 / 5	0.53	-0.40	1.47	3.7

Model	Overall Weighted Effect Size	*SE*	Confidence Level (95%)	*Q* Statistic	I^2	T^2	Classic Fail-Safe *N*
Random	0.61	0.10	0.41 − 0.81	18.42	13.15	0.02	163

Abbreviations. atDCS: anodal transcranial current stimulation; BBS: Berg Balance Scale; cH: contralesional hemisphere; CI: confidence interval; CIMT: constraint-induced movement therapy; ctDCS: cathodal transcranial direct current stimulation; FMA: Fugl-Myer assessment; iH: ipsilesional hemisphere; NIHSS: National Institutes of Health Stroke Scale; OT: occupational therapy; PNS: peripheral nerve stimulation; PPT: Purdue Pegboard Test; PT: physical therapy; RGO: robotic gait orthosis; rTMS: repetitive transcranial magnetic stimulation; Rx: treatment group; SE: standard error; SMD: standardized mean differences

Measuring heterogeneity and publication bias

Cochran's *Q*, Higgins and Green's I^2, and T^2 (estimate of tau-squared) estimated heterogeneity between the studies. Determining heterogeneity is vital for the meta-analytic technique.[42 43] I^2 represents heterogeneity as percentage values to assess evidence as different than a statistical chance occurrence.[44] Higgins and Green reported that greater than 50% of I^2 indicates substantial heterogeneity (inconsistency).[43] T^2 is an estimate of variance of the true effects sizes in a random effects model.[41] A T^2 greater than 1.0 denotes substantial heterogeneity between studies.

We examined publication bias with three statistical procedures that were consistent with traditional meta-analysis:[45 46] (a) funnel plot showing the symmetry of the studies (standardized mean differences versus standard error for each study),[43 47] (b) trim and fill technique for generating a subsequent funnel plot with imputed values to estimate an unbiased distribution,[48] and (c) classic fail-safe *N* analysis to determine the number of studies necessary to decrease the overall effect size to an insignificant level.[49]

RESULTS

Standardized mean difference effect

A random effects model meta-analysis on the 17 comparison studies showed a significant overall standardized mean difference effect equal to 0.61 ($SE = 0.10$; $p < 0.0001$; $Z = 5.99$; 95% CI = 0.41 − 0.81). This is a positive medium effect size.[42] Table 4 displays each effect size (*ES*): minimum = 0.04 and maximum = 1.59. No individual weighted effect exceeded two standard deviations of the standardized mean effect size. Further, all studies revealed positive effect sizes as shown in the forest plot (Figure 1). These robust findings indicate that tDCS improved motor

learning post stroke across stimulation protocols and stages of recovery. Moderator variable analyses provide further insights.

Insert Figure 1 about here

Heterogeneity and publication bias

Variability measures on our 17 studies revealed low heterogeneity: Q = 18.42 and p = 0.30; I^2 = 13.15%; T^2 = 0.02; Table 4. Visual inspection of the funnel plot shows a relatively symmetrical distribution of each effect size over the 17 studies (minor publication bias; Figure 2). Applying the trim and fill method[48] produced an identical overall effect size (see Figure 2: black diamond; no trimmed studies) in comparison to the original (see Figure 2: white diamond). Moreover, a classic fail-safe N analysis indicated that 163 null effect findings are required for decreasing our significant overall effect size (0.61; $p < 0.0001$) to an insignificant level ($p > 0.05$). Consequently, these combined findings support a minor publication bias conclusion.

Insert Figure 2 about here

Moderator variable analyses

A. Stimulation protocols

The first moderator variable analysis investigated the effectiveness of three stimulation protocols on motor learning post stroke: (a) anodal stimulation on M1 of ipsilesional hemisphere, (b) cathodal stimulation on M1 of contralesional hemisphere, and (c) bilateral stimulation. Seven anodal stimulation studies revealed an overall ES = 0.47 (SE = 0.21; p = 0.03; Z = 2.22; 95% CI = 0.06 − 0.88; I^2 = 41.52%; T^2 = 0.12) whereas five cathodal stimulation studies showed an overall ES = 0.74 (SE = 0.17; $p < 0.0001$; Z = 4.30; 95% CI = 0.40 − 1.08; I^2 = 0.00%; T^2 = 0.00).

Analysis of the five bilateral stimulation studies indicated an overall *ES* = 0.69 (*SE* = 0.15; $p < 0.0001$; Z = 4.50; 95% CI = 0.39 − 0.99; $I^2 = 0.00\%$; $T^2 = 0.00$). Taken together, these findings indicate beneficial effects of tDCS on motor learning post stroke for each of the three stimulation protocols.

B. Stage of recovery post stroke

In a second moderator analysis, we compared the long-term motor learning effects of tDCS based on three stages of post stroke recovery. However, only two acute studies were available in our meta-analysis. Rather than report a spurious finding for the acute phase, we did not analyze the earliest stage post stroke. Analysis on the two subsequent stages showed a significant overall effect size for the chronic stage (11 studies): *ES* = 0.68 (*SE* = 0.11; $p < 0.0001$; Z = 6.24; 95% CI = 0.47 − 0.89; $I^2 = 0.00\%$; $T^2 = 0.00$). Four sub-acute stage studies revealed an insignificant overall *ES* = 0.76 (*SE* = 0.44; $p = 0.08$; Z = 1.73; 95% CI = -0.10 − 1.62; $I^2 = 72.10\%$; $T^2 = 0.53$). The findings indicate that long-term motor learning effects of tDCS predominantly appeared in chronic stroke patients.

C. Stimulation timing

A third moderator analysis examined the effects of stimulation timing on motor learning. Direct comparison of stimulation before versus during motor training involved all 17 studies. Seven studies that provided stimulation before motor training indicated an overall *ES* = 0.64 (*SE* = 0.17; $p < 0.0001$; Z = 3.73; 95% CI = 0.31 − 0.98; $I^2 = 19.12\%$; $T^2 = 0.04$). Ten studies used tDCS protocol during motor training revealed a significant overall *ES* = 0.59 (*SE* = 0.14; $p < 0.0001$; Z = 4.36; 95% CI = 0.32 − 0.85; $I^2 = 16.62\%$; $T^2 = 0.03$). The results clearly indicate long-term motor improvements when tDCS is provided either before or during motor training.

DISCUSSION

This focused systematic review and meta-analysis determined the long-term motor learning effect post stroke after treatment of tDCS protocols combined with motor training. We investigated the effects of three tDCS protocols on relatively permanent changes in motor actions for individuals who experienced a stroke across the three stages of recovery: acute, sub-acute, and chronic. Making progress toward restoring motor actions by measuring motor learning improvements from baseline to long-term retention testing is crucial for understanding functional recovery of stroke survivors. Together, the meta-analytic techniques conducted on the 17 comparison studies support the conclusion that the tDCS protocols showed long-term beneficial effects on motor actions post stroke. These significant, positive, and robust tDCS findings revealed substantial motor learning improvements for individuals in the chronic stage of recovery. Moreover, the tDCS protocols provided either before or during motor training revealed beneficial long-term effects on motor functions post stroke.

Previous stroke narrative reviews reported evidence that tDCS improved motor functions immediately after intervention, and long-term tDCS benefits were missing.[3 11 50] Several systematic reviews found that the motor improvement evidence after tDCS intervention persisted at long-term follow-up testing.[13 19] Further, two recent stroke meta-analyses indicated that long-term motor improvements after tDCS are still controversial.[14 20] Perhaps, the small sample of studies (e.g., two or three studies) as well as including studies that used tDCS protocols without motor training contributed to debatable motor learning benefits. However, our significant medium overall effect size (0.61) with 17 long-term retention findings after coupled tDCS and motor training strongly support the proposition that motor functions improved by tDCS interventions remained relatively permanent (i.e., mean = 41.1 days and SD = 44.8 days).

As predicted, three significant effect sizes from each stimulation protocol indicated that the three tDCS protocols contribute to long-term motor learning improvements post stroke. Moreover, the pattern of smaller effect size found in anodal stimulation (*ES* = 0.47) in comparison to cathodal stimulation (*ES* = 0.74) and bilateral stimulation (*ES* = 0.69) was consistent with patterns in transient motor improvements[14 51 52] and relatively permanent motor improvements.[13] Specifically, Ludemann-Podubecka *et al*[13] reported different motor learning outcomes based on the three tDCS protocols: (a) anodal: 14% of all stroke patients, (b) cathodal: 43%, and (c) bilateral: 62%. These cumulative findings indicate that suppressing activity in the contralesional hemisphere after tDCS protocols (i.e., cathodal and bilateral stimulations) may be more effective for long-term motor improvements post stroke than only anodal stimulation.

One possible interpretation concerning the smaller effect size of anodal stimulation on motor learning may involve impaired neural plasticity in the ipsilesional hemisphere in comparison to the contralesional hemisphere. Some aging studies have proposed that the smaller motor improvements observed in elderly adults from tDCS than young adults may be attributed to a decreased capability for neuroplastic changes in response to NIBS with advancing age.[53 54] Indeed, Fujiyama *et al*[54] reported that cortical excitability changes in response to anodal stimulation were delayed in an elderly group relative to a young group. Consequently, a constrained capability for neuroplasticity in the ipsilesional hemisphere may cause less motor learning efficacy in comparison to the other protocols stimulating the motor area in the contralesional hemisphere.

Beneficial long-term motor learning effects only appeared in chronic recovery stage post stroke. These results are consistent with two previous systematic reviews and meta-analyses in that significant motor improvements post tDCS interventions are most evident in the chronic

stage of recovery.[13 14] Based on the interhemispheric competition model, 17 qualified studies used anodal stimulation on ipsilesional hemisphere, cathodal stimulation on contralesional hemisphere, or bilateral stimulation for all stroke participants who may have different impairment severity, lesion location (e.g., cortical and subcortical), or recovery stage (e.g., acute, sub-acute, and chronic). However, uniform tDCS protocols applied to different levels of stroke severity may cause inter-individual variability in the rehabilitation efficacy.[55 56]

To minimize inter-individual variability in tDCS protocols, the bimodal balance-recovery model proposed by Di Pino *et al*[56] incorporates the two recovery models: (a) vicariation and (b) interhemispheric competition. Contrary to the interhemispheric competition model, the vicariation model has a positive view on the activation in contralesional hemisphere for rehabilitation. Assuming that brain activation in the contralesional hemisphere serves as compensatory activity that contributes to functional recovery of paretic limbs,[57] cathodal stimulation decreasing brain activation in the contralesional hemisphere may cause counterproductive effects in stroke survivors. Hummel and colleagues stated that cathodal stimulation on the contralesional hemisphere is disadvantageous for some stroke patients because brain activity patterns in the contralesional hemisphere were activated while executing paretic hand movements for some patients.[58-60] On the other hand, the newly proposed bimodal balance-recovery model introduces structure reserve, the quantity of strategic neural pathways and relays spared by the lesion. Higher structure reserve typically indicates better motor recovery.[56] Further, the structure reserve may be affected by impairment severity, lesion location, and recovery stage. The bimodal balance-recovery model posits that the vicariation model accurately predicts recovery for patients with lower structure reserve (e.g., more extensive stroke region and severe damage) whereas the interhemispheric competition model is more appropriate for patients with

higher structure reserve (e.g., smaller stroke region and less severe damage). Thus, the behavioral benefits from three types of tDCS protocols based on the interhemispheric competition model may decrease for patients with lower structure reserve. In line with previous findings, the significant motor learning effect size found for our chronic group indicates that recovery stage may influence the structure reserve causing inter-individual variability in the efficacy of uniform tDCS protocols.

A third moderator variable analysis showed that both tDCS before and during motor training significantly facilitate long-term motor improvements post stroke. The effect size found for stimulation before motor training (*ES* = 0.64) was slightly greater than stimulation during motor training (*ES* = 0.59). However, the optimal timing of tDCS (i.e., before versus during motor training) is still open question. Giacobbe and colleagues reported that movement smoothness improved when tDCS was applied before movement training whereas no improvement was found in tDCS during movement training.[61] On the other hand, Stagg and colleagues reported slower motor learning when both anodal and cathodal stimulations were provided before the motor learning task.[62] Given that brain activation mechanisms are different depending on stimulation onset,[63 64] more studies investigating the order of tDCS protocols while applying motor training will be necessary for maximizing motor learning effects post stroke.

Despite the robust motor learning effects of tDCS protocols on arm movements post stroke, the number of studies focusing on lower extremity functions as well as the acute recovery stage is limited. These findings indicate that long-term motor learning effects of tDCS are still debatable for the lower extremities and early recovery stage post stroke.[3 13] Conducting more long-term follow-up testing for lower extremity functions as well as the acute recovery stage may consolidate rehabilitative effects of tDCS interventions.

In conclusion, this systematic review and meta-analysis provides convincing evidence supporting a conclusion that active tDCS positively facilitated long-term motor learning in stroke individuals. Moreover, moderator variable analyses showed that the benefits of tDCS on motor learning were slightly different based on stimulation protocols. The significant effect size found in the chronic stage may indicate inter-individual variability in the efficacy of tDCS protocols depending on the interhemispheric competition model.[56] Additional tDCS studies investigating motor learning effects based on different structure reserve representations will be necessary for researchers to develop individualized tDCS protocols. Further, given that brain imaging studies confirm that transient motor improvements correlate with brain activation patterns modulated by tDCS,[65-67] there is a need to investigate brain activation changes during tDCS-induced motor learning to identify the neurological mechanisms underlying long-term functional recovery post stroke.

Author Contributions

NK independently extracted relevant data from the 17 studies and coded the outcome measures. Two authors (JJS & JHC) confirmed the extracted data. Each author contributed to interpreting the meta-analytic results, manuscript drafts, and approved revisions and the final manuscript.

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Competing Interests

None

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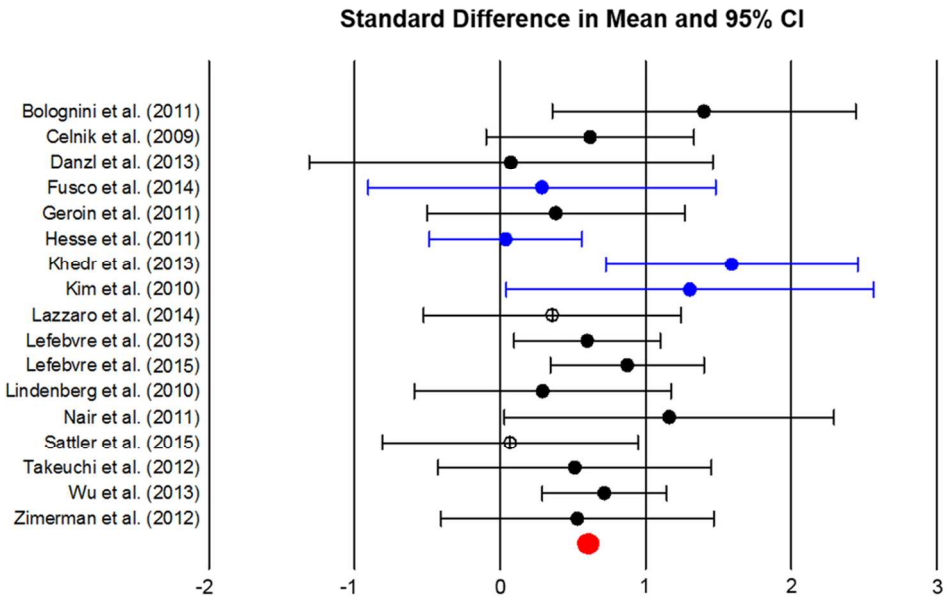
Figure Captions

Figure 1. Meta-analysis forest plot of the effects of tDCS on motor learning post stroke. Data derived from a random effects model. Each line and tick mark represents an individual effect size. The red circle indicates an overall effect size (0.61). Note: black = chronic; blue = sub-acute; white = acute.

Figure 2. Funnel plot of the comparisons for random effects model. The x-axis represents the standardized mean difference and the y-axis indicates the standard error associated with each comparison. The white diamond indicates overall effect size with our original 17 comparisons and the black diamond indicates a revised overall effect size after the trim and fill procedure.



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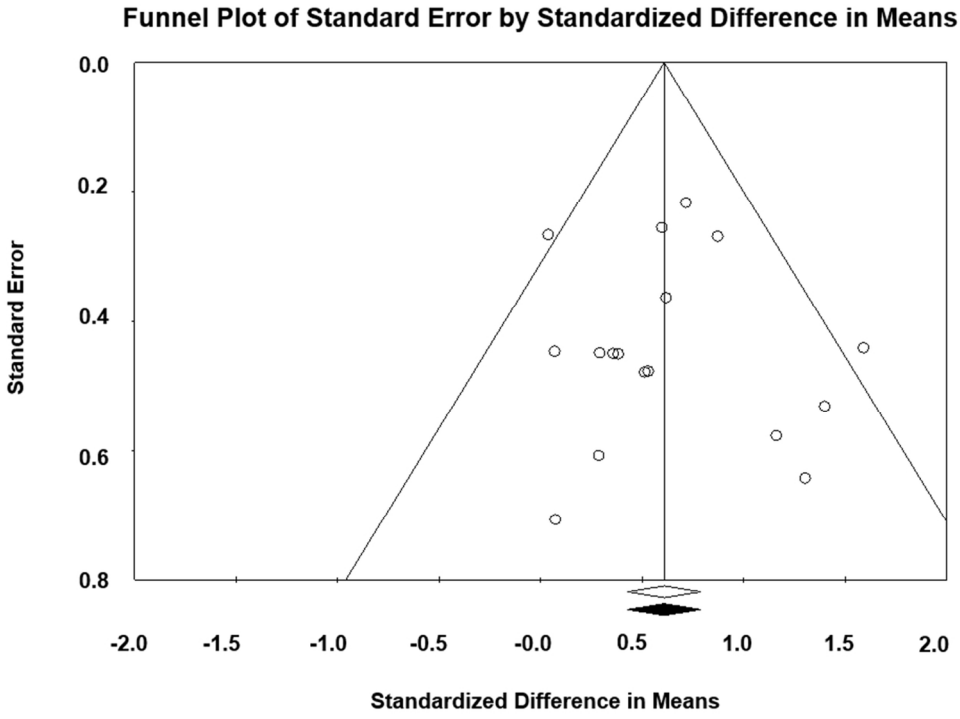
48x31mm (600 x 600 DPI)



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55x40mm (600 x 600 DPI)