Transcranial direct current stimulation for improving ambulation after stroke: a systematic review and meta-analysis

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Achieving a sufficient level of functional ambulation remains to be a challenge to most stroke survivors. Different modes of transcranial direct current stimulation (tDCS) have been applied for improving various aspects of walking and mobility following stroke. However, systematic reviews before 2017 provided only general effects of tDCS on limited walking outcomes. Therefore, the aims of this study were to update the evidence of tDCS for improving walking and mobility after stroke with emphasis on individual outcomes and to delineate the effects of different modes of tDCS in subgroup analysis. The systematic search of PubMed, Medline, PEDro, Scopus, and Cochrane databases for studies published up to January 2019 identified 14 eligible reports. The PEDro scale indicated a good methodological quality of the included studies (score 6.8). The meta-analysis of primary outcomes revealed that active tDCS had no better effect than sham on walking speed [n = 7, standardized mean difference (SMD) = 0.189, *P* = 0.252] and 6-minute walking distance (n = 3, SMD = 0.209, *P* = 0.453). Among the secondary outcomes, significant positive effects were found on functional ambulation category (FAC) (n = 5, SMD = 0.542, *P* = 0.008), Rivermead Mobility Index (n = 3, SMD = 0.699, *P* = 0.008), and timed up and go test (TUG) (n = 5, SMD = 0.676, *P* = 0.001), whereas non-significant positive effects were found on Tinetti test (n = 3, SMD = 0.441, *P* = 0.062) and Berg Balance Scale (n = 2, SMD = 0.408, *P* = 0.177). In subgroup analyses, anodal tDCS had significant positive effects on FAC (n = 4, SMD = 0.611, *P* = 0.005) and dual-hemispheric tDCS on TUG (n = 2, SMD = 1.090, *P* = 0.000). The results provide up-to-date evidence of variable effects of tDCS on walking and functional mobility after stroke. *International Journal of Rehabilitation Research* **43: 299–309**

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Introduction

Stroke is a leading cause of disability and morbidity associated with substantial economic costs for post-stroke care (Rajsic *et al.*, 2019). More than 50% of patients with chronic stroke live with motor dysfunctions (Charvet *et al.*, 2015). Among them, ambulation difficulty has been identified as one of the major functional deficits in stroke survivors (Winstein *et al.*, 2016). Furthermore, walking with optimal velocity and endurance to support functional ambulation remains to be a challenge to most of the stroke survivors and rehabilitation personnel (Eng and Tang, 2007).

Transcranial direct current stimulation (tDCS), a noninvasive electrical stimulation technique has been extensively investigated for its effects on stroke recovery (Bastani and Jaberzadeh, 2012; Elsner *et al.*, 2016; Li *et al.*, 2018). The low-intensity current of tDCS is able to modulate the membrane potential of cortical neurons and to induce long-term potentiation-like plasticity in motor cortex (Paulus *et al.*, 2012; Filmer *et al.*, 2014). With a single pair of electrodes, tDCS elicits different physiological effects depending on its configurations over lesioned or non-lesioned sides of the brain (Nitsche and Paulus, 2000). To improve motor recovery after stroke, tDCS is expected to balance the abnormal interhemispheric interaction, decrease the maladaptive plasticity of the affected brain (Fregni and Pascual-Leone, 2007), and enhance motor learning during rehabilitation (Kang *et al.*, 2016). At large, the effects of anodal and cathodal tDCS on motor recovery of the upper extremity for stroke patients have been revealed by many systematic reviews and meta-analyses (Bastani and Jaberzadeh, 2012; Tedesco Triccas *et al.*, 2016; Chhatbar *et al.*, 2016). However, compared to the evidences available for effects of tDCS on the function of upper extremity, evidences on the recovery of lower extremity and ambulation ability are relatively scarce.

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A recent meta-analysis allocating randomized controlled trials published before 2017 revealed a significant effect of tDCS on improving general mobility but not on walking speed and endurance (Li *et al.*, 2018). However, the positive effect on general mobility was based on analysis of pooled outcome measures [timed up and go (TUG) test, Tinetti test, and functional ambulatory category (FAC)] with diverse measurement properties among studies. Moreover, it was not clear which outcome was selected as an index of mobility for certain trials with multiple outcomes. Furthermore, owing to limited number of trials available for analysis, some of the effects of tDCS were mixed with the effects of transcutaneous spinal direct stimulation (tsDCS) (Picelli *et al.*, 2015). Therefore, evidences to the effect of tDCS on ambulation ability after stroke remain inconclusive and require update. In addition, clinicians have adopted dual-hemispheric or bihemispheric tDCS more frequently to enhance motor recovery after stroke (Lindenberg *et al.*, 2010; Mahmoudi *et al.*, 2011). Therefore, the effects of different modes of tDCS should be delineated when evidences become available. For these reasons, the aims of this study were to investigate the effects of tDCS for improving ambulation ability with outcome representing different aspects of walking ability and to perform subgroup analysis to delineate the effects of different modes of tDCS on improving ambulation ability following stroke.

Methods

Literature search strategy

The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) was used to guide this systematic review and meta-analysis (Moher *et al.*, 2009). To allocate eligible studies published until January 2019, a literature search was performed using the following databases: PubMed, Medline, PEDro, Scopus, and Cochrane. The key search terms were: ('transcranial direct current stimulation' or 'tDCS') AND ('stroke[Mesh]') AND ('gait' or 'ambulation' or 'locomotion'). Two reviewers independently identified the relevant studies according to the inclusion and exclusion criteria and progressively retrieved the suitable studies.

Selection criteria

The published articles matched the following criteria would be included: (1) application of tDCS in patients with stroke who were over 18 years of age; (2) outcome assessments including gait parameters, walking speed and endurance, functional mobility test or questionnaire for walking ability and balance; (3) pre-post and randomized controlled clinical study design; (4) active tDCS versus sham tDCS and could combine other rehabilitation treatments in two groups; (5) published in English or Chinese language. Studies were excluded if: (1) patients had other types of neurological or musculoskeletal diseases or subjects were non-human subjects; (2) treatment combined other types of stimulation; (3) the articles were non-clinical trials including review, case report, editorial comment, and meta-analysis. Two reviewers independently screened the studies by reading titles and abstracts of the extracted studies. If the abstracts were ambiguous and had no sufficient details, reviewers would read the full text to make the final decision. Different decisions between reviewers were resolved by consensus.

Quality assessment

Quality assessment was conducted by using the Physiotherapy Evidence Database (PEDro) scale to evaluate the methodological quality of the eligible studies (Moseley *et al.*, 2002). The PEDro scale consists of 10 ratings to assess the methodological quality of a clinical study. Total PEDro score ranges from 0 to 10. Scores ranging from 10-9, 8-6, and 5-4 on the PEDro scale have been considered as 'excellent', 'good', and 'fair' quality. Studies scoring below four are considered as 'poor' (Foley *et al.*, 2003). Furthermore, the strength of evidence for the therapeutic measure was assessed according to Guidelines for Management of Ischemic, Transient Ischemic and Intracranial Hemorrhage from The European Stroke Organization (ESO) (European Stroke Organisation (ESO) Executive Committee, ESO Writing Committee, 2008). Two reviewers independently graded the PEDro score of the individual studies. Different scores between reviewers were resolved by consensus or by discussing with the third independent reviewer.

Outcome measures

The effects of tDCS for ambulation were involved in extracting the primary and secondary outcomes from eligible studies. The primary outcomes in this meta-analysis were defined as walking speed and endurance. The walking speed was derived from 10-Meter Walking Test or by other quantitative gait analysis and the walking endurance was represented by 6-Minute Walking Test (6MWT). The secondary outcomes were related to functional mobility and balance assessed by functional ambulation category (FAC), Tinetti test [Performance Oriented Mobility Assessment (POMA)], Rivermead Mobility Index (RMI), TUG test, and Berg Balance Scale (BBS) (Salter *et al.*, 2013; Canbek *et al.*, 2013). However, if the required data of the outcome measures were unavailable even after contacting the corresponding author, we would extract the results but not include the data into the meta-analysis.

Data extraction

After two reviewers screened the studies according to the inclusion/exclusion criteria, the following data and descriptive information relevant to the aims of this study were extracted: (1) study design; (2) characteristics of the study, including the number and age of subjects, stroke type, affected side and stroke duration; (3) parameters of tDCS and treatment protocols including the mode of application, size of electrode, the placement of electrode,

current intensity and density; (4) outcomes for both pre- and post-treatment in active and sham tDCS groups; (5) harm or adverse effects.

Statistical analysis

The meta-analysis was conducted by using comprehensive meta-analysis (ver. 3.0; Biostat, Englewood, New Jersey, USA). The standardized mean differences (SMDs) derived from changing scores of post- and pre-treatment between active and sham tDCS groups were adopted as the measure of effect size. The correlation coefficient between pre- and post-treatment was inputted ($r = 0.7$) as a conservative estimate according to the recommendation by Rosenthal (1991). For the cross-over study, we extracted the data from the first period only (Elbourne *et al.*, 2002). In addition, the heterogeneity in outcome was tested by the Q statistic and the I^2 test. When P values in Cochrane's Q test were less than 0.10 and I^2 values were greater than 50%, it showed significant heterogeneity and a random effect model was adopted to adjust for variance (Higgins and Thompson, 2002; Higgins and Green, 2011). Otherwise, the fixed-effect model was used. In the subgroup analysis, the effects of different stimulation modes were investigated for the possible post-hoc subgroup effect. Studies were grouped into anodal, cathodal, and dual-hemispheric tDCS for further analyses. $P < 0.05$ was considered a statistical significance of each meta-analysis.

Results

Identification and selection of studies

After removing the duplicated studies, screening the titles, abstracts, and full-text reviewing the 143 studies identified through database searching, 14 studies were extracted for the final analysis. The PRISMA flowchart (Fig. 1) showed the searching and extracting process with results. Among the 14 studies included in the final analysis, 13 of them were randomized controlled trials. Five studies adopted cross-over design (Table 2) (van Asseldonk and Boonstra, 2016; Saeys *et al.*, 2015; Klomjai *et al.*, 2018; Manji *et al.*, 2018; Utarapichat and Kitisomprayoonkul, 2018). However, two of the 14 studies (Danzl *et al.*, 2013; van Asseldonk and Boonstra, 2016) did not reply upon the data request. The data reported by Danzl *et al.* (2013) were marked in figures only and had been extracted by a plot digitizer program (Plot Digitizer, 2015) in a meta-analysis (Li *et al.*, 2018). However, with overlapped means and SDs on the figures, we were not confident to extract data directly from those figures without confirmations from authors (Danzl *et al.*, 2013). Therefore, the results of those two studies were excluded from the meta-analysis.

Quality assessment of the studies

The PEDro score of the included 14 studies ranged from 5 to 9 with a mean score of 6.8, which indicated a good methodological quality of the included studies (Foley *et al.*, 2003). Besides, six of those studies were ranked as the highest level of evidence (class I) and all other studies were ranked as class II by the classification system of ESO (European Stroke Organisation (ESO) Executive Committee, ESO Writing Committee, 2008). The rating of PEDro scale and level of evidence for each study were presented in Table 1.

Participants in the included studies

The 14 studies extracted in this review included a total of 266 patients with stroke. The stroke duration ranged from 16 days to 152.5 months which comprised patients from acute to chronic stage of recovery. The major cause of stroke was an ischemic type including 199 patients and 47 patients were the hemorrhagic type. One of the studies (n = 20) did not provide the information about the type of stroke patients (Cha *et al.*, 2014). Overall, a total of 248 patients were allocated in the final meta-analysis. The characteristics of participants for each study were illustrated in Table 2.

Parameters of transcranial direct current stimulation in the included studies

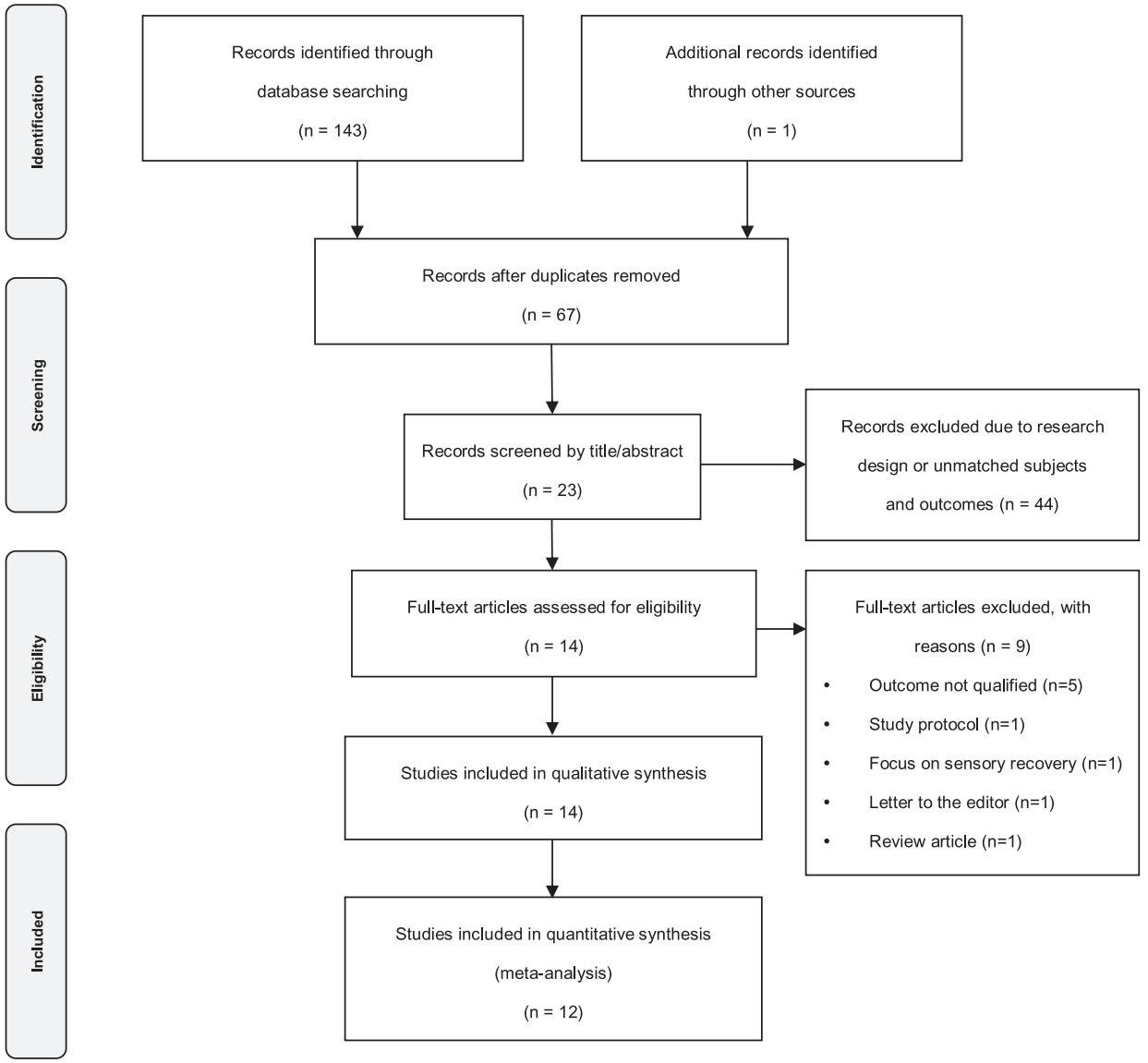
The mode of tDCS application was determined by arrangement of the position and polarity of the electrodes over ipsilesional or/and contralesional side of brain. In the included studies, nine studies used anodal tDCS and one study used cathodal tDCS, while three studies used dual-hemispheric stimulation by putting anode on ipsilesional and cathode on contralesional side of brain. The placement of electrode in anodal mode was to place the anode overlying the motor cortex of the leg area which centered on a short distance lateral to Cz or on C3/C4. The reference electrode was put on the contralateral supraorbital region near Fp1/Fp2 in most of the studies.

Among the included studies, nine used a current intensity of 2 mA, three used 1.5 mA, and two used 1 mA for treatment. As for the size of electrode, most of the trials used a 35 cm^2 sponge electrode as an active electrode (Paulus *et al.*, 2012). The current density of tDCS applications ranged from 0.029 to 0.08 mA/cm^2 while 0.057 mA/cm^2 was the most commonly used current density. Eight of the included studies did not provide the fade-in and fade-out settings of the tDCS. Other studies faded in and faded out the current gradually from 5 to 30 seconds. The parameters of tDCS application were listed in Table 3.

Treatment programs along with transcranial direct current stimulation

In addition to active and sham tDCS, there were six studies providing additional treatment with tDCS related to ambulation training (Table 2). Among them, three studies used robot-assisted gait training as rehabilitation programs (Geroin *et al.*, 2011; Leon *et al.*, 2017; Seo *et al.*, 2017). One study used robotic gait orthosis (RGO) for locomotion training (Danzl *et al.*, 2013) and the other

Fig. 1



The PRISMA flowchart of the searching process.

studies used either task-related training (Park *et al.*, 2015) or body weight-supported treadmill training (Manji *et al.*, 2018) to treat gait disturbance after stroke. Besides, four studies provided tDCS simultaneously during the treatment program (Geroin *et al.*, 2011; Park *et al.*, 2015; Leon *et al.*, 2017; Manji *et al.*, 2018) while two studies applied tDCS before interventions (Danzl *et al.*, 2013; Seo *et al.*, 2017).

Adverse events

Among 14 studies, two studies reported some of the adverse events associated with tDCS (Leon *et al.*, 2017; Klomjai *et al.*, 2018). Among them, with patients in both studies reported transitory itching and tingling during tDCS. In addition, one subject experienced mild headache after tDCS and resolved without any treatment within 24 h (Klomjai *et al.*, 2018). Furthermore, one patient was excluded due to mild headache during and after stimulation (Leon *et al.*, 2017). According to the Common Terminology Criteria for Adverse Events, the above results suggested tDCS may cause mild to moderate adverse events (grades 1 and 2) which involved mild symptoms with or without medical treatment (Antal *et al.*, 2017). However, the reports of adverse events were inconsistent in the included studies. Five of them reported no adverse effect associated with tDCS (Geroin *et al.*, 2011; Danzl *et al.*, 2013; Tahtis *et al.*, 2014; Saeys *et al.*, 2015; Utarapichat and Kitisomprayoonkul, 2018) while seven

Table 1 PEDro scale for quality assessment and level of evidence by the European Stroke Organization in the included studies

Study	1	2	3	4	5	6	7	8	9	10	11	Total	Quality	LoE
Geroin *et al.* (2011)	√	√		√			√	√		√	√	6	Good	Class I
Danzl *et al.* (2013)	√	√		√	√		√			√		5	Fair	Class II
Cha *et al.* (2014)	√	√						√	√	√	√	5	Fair	Class II
Fusco *et al.* (2014)	√	√		√	√		√			√	√	6	Good	Class II
Tahtis *et al.* (2014)	√	√		√	√		√	√	√	√	√	8	Good	Class I
Chang *et al.* (2015)	√	√		√	√	√	√	√	√	√	√	9	Excellent	Class I
Park *et al.* (2015)	√	√						√	√	√	√	5	Fair	Class II
Saeys *et al.* (2015)	√	√	√	√	√	√	√	√		√	√	9	Excellent	Class I
van Asseldonk and Boonstra (2016)	√	√			√	√		√		√	√	6	Good	Class II
Leon *et al.* (2017)	√			√	√	√		√		√	√	6	Good	Class II
Seo *et al.* (2017)	√	√		√	√	√	√	√	√	√	√	9	Excellent	Class I
Klomjai *et al.* (2018)	√	√		√		√	√	√	√	√	√	8	Good	Class I
Manji *et al.* (2018)	√	√		√	√			√	√	√	√	7	Good	Class II
Utarapichat and Kitisomprayoonkul (2018)	√	√			√			√	√	√	√	6	Good	Class II

ESO, European Stroke Organization; LoE, level of evidence; PEDro scale, Physiotherapy Evidence Database scale.

studies did not provide such information (Cha *et al.*, 2014; Fusco *et al.*, 2014; Chang *et al.*, 2015; Park *et al.*, 2015; van Asseldonk and Boonstra, 2016; Seo *et al.*, 2017; Manji *et al.*, 2018).

Quantitative data synthesis

Among all of the meta-analysis, the only marginal heterogeneity was found on the effect of dual-hemispheric tDCS on Tinetti test in subgroup analysis (I^2 = 52.065%). Therefore, only that effect was analyzed by the random effect model and the rest of analyses adopted the fixed effect model.

In the analyses of the primary outcomes, active tDCS did not improve walking speed [n = 7; SMD: 0.189, 95% confidence interval (CI) –0.135 to 0.513, P = 0.252] and 6MWT (n = 3; SMD: 0.209, 95% CI –0.338 to 0.756, P = 0.453) better than the sham tDCS (Fig. 2).

In the analyses of the secondary outcomes, significant and beneficial effects of active tDCS were found on FAC (n = 5; SMD = 0.542, 95% CI 0.142–0.942, P = 0.008), RMI (n = 3; SMD = 0.699, 95% CI 0.180–1.219, P = 0.008), and TUG (n = 5; SMD = 0.676, 95% CI 0.293–1.058, P = 0.001). However, the effects on Tinetti test (n = 3; SMD = 0.441, 95% CI –0.022 to 0.904, P = 0.062) and BBS (n = 2; SMD = 0.408, 95% CI –0.184 to 0.999, P = 0.177) were both insignificant but in favor of the active tDCS than the sham tDCS (Fig. 2).

When the effects of tDCS were further analyzed according to the mode of application, significant effects of anodal tDCS on FAC (n = 4; SMD = 0.611, 95% CI 0.186–1.036, P = 0.005) and dual-hemispheric tDCS on TUG (n = 2; SMD = 1.090, 95% CI 0.507–1.672, P = 0.000) were extracted from subgroup analyses (Fig. 2).

Discussion

In this study, we evaluated the effects of tDCS on the recovery of ambulation ability in patients with stroke. Meta-analysis on studies with proper design and methodological quality revealed positive effects of active tDCS in half of the outcomes measuring walking ability (3/6). Essentially, FAC, RMI, and TUG improved significantly following active tDCS (effect sizes: 0.542–0.687). However, tDCS had non-significant effects on walking speed, walking endurance (6MWT), and Tinetti test. Yet, all these effects were in favor of the active tDCS rather than sham tDCS. Similarly, active tDCS could not effectively improve BBS. Furthermore, subgroup analyses revealed that, anodal tDCS had significant effect on FAC (n = 4; effect size = 0.611) while dual-hemispheric tDCS improved TUG (n = 2; effect size = 1.090) significantly (Fig. 2f).

Results of this meta-analysis provide up-to-date evidence that tDCS has the beneficial effects to restore walking ability and functional mobility following stroke. After stroke, decreased excitability of the motor cortex owing to lesion of the affected brain or unbalanced transcallosal inhibition or both have been documented for decades (McDonnell and Stinear, 2017). Thus, tDCS was expected to balance the excitability between two hemispheres after brain lesion (Fregni and Pascual-Leone, 2007; Gomez Palacio Schjetnan *et al.*, 2013). The study has revealed that unilateral anodal tDCS applied on the leg area of the primary motor cortex of the affected hemisphere during walking could increase excitability of the motor cortex while simultaneously decrease excitability of the unaffected side (Jayaram and Stinear, 2009). It is feasible to stimulate the leg area of the primary motor cortex which is located in the edge of the hemisphere and the mesial surface in the median longitudinal fissure (Penfield and Boldrey, 1937). In addition, meta-analysis showed that tDCS improved muscle strength of lower limb in stroke (Li *et al.*, 2018) and increased the activity of motor cortex involved in learning (Madhavan and Shah, 2012). Thus, tDCS was expected to be able to improve the walking ability following stroke.

Compared to the most recent meta-analysis on the effects of tDCS on walking after stroke (Li *et al.*, 2018) which allocated 10 studies (n = 194) published between 2011 and 2016 into analysis, four of these studies were excluded from our analysis owing to that the effect of

Table 3 Treatment protocol of transcranial direct current stimulation

Study ID	UNI/DUAL	iH	cH	Anode	Cathode	Intensity (mA)	Size (cm^2)	Duration (min)	Session	Current density (mA/cm^2)	Fade-in/fade-out
Geroin *et al.* (2011)	UNI	A	–	(leg area)[a]	CSR[a]	1.5	35	7	10	0.043	NA
Danzl *et al.* (2013)	UNI	A	–	Motor area (leg area) [a]	CSR[a]	2	A:25/C:35	20	12	0.08/0.057	Fade in and out over first 75 seconds (sham tDCS)
Cha *et al.* (2014)	UNI	A	–	PMC (C3 or C4)	Forehead[a]	1	35	20	20	0.029	NA
Fusco *et al.* (2014)	UNI	–	C	Noncephalic side[b]	PMC (C3' or C4')	1.5	35	10	10	0.043	Gradually increased and progressively reduced
Tahtis *et al.* (2014)	DUAL	A	C	Bilateral MC over 5 mm lateral to Cz (leg area)		2	25	15	1	0.08	Fade in less than 30 seconds (sham tDCS)
Chang *et al.* (2015)	UNI	A	–	TA area of the PG[a]	CSR[a]	2	A:7.07 C:28.26	10	10	0.283/0.071	NA
Park *et al.* (2015)	UNI	A	–	Cz area of the left PL	Right upper orbit[a]	2	–	15	12	–	NA
Saeys *et al.* (2015)	DUAL	A	C	MC (C3 or C4)		1.5	35	20	16	0.043	Fade in for 5 seconds/Fade out last 5 seconds (both groups)
van Asseldonk and Boonstra (2016)	UNI	A	–	Hotspot of TA by TMS[a]	CSR[a]	2	35	10	1	0.057	Fade in for 30 seconds (sham tDCS)
	DUAL	A	C	Hotspot of TA shifted laterally 1 cm[a]		2	35	10	1	0.057	
Leon *et al.* (2017)	UNI	A	–	Leg: vertex (Cz)	CSR[a]	2	35	20	20	0.057	NA
Seo *et al.* (2017)	UNI	A	–	Lateral to Cz	CSR[a]	2	35	20	10	0.057	NA
Klomjai *et al.* (2018)	DUAL	A	C	Bilateral PMC placed 5 mm lateral from vertex (Cz)		2	35	20	1	0.057	NA
Manji *et al.* (2018)	UNI	A	–	3.5 cm anterior to Cz (SMA)	Inion[a]	1	25	20	7	0.04	NA
Utarapichat and Kitisomprayoonkul (2018)	UNI	A	–	1 cm posterior and lateral to Cz	CSR[a]	2	10	10	1	0.2	Fade in for 10 seconds/fade out for 10 seconds (both groups)

A, anodal tDCS; C, cathodal tDCS; cH, contralesional hemisphere; CSR, contralateral supraorbital region; DUAL, dual-hemispheric tDCS; iH, ipsilesional hemisphere; MC, motor cortex; NA, not available; PG, precentral gyrus; PL, parietal lobe; PMC, primary motor cortex; SMA, supplementary motor area; TA, tibialis anterior; TMS, transcranial magnetic stimulation; UNI, uni-hemispheric tDCS.

[a]No description according to 10/20 system.

[b]Noncephalic side is located above the right shoulder, contralateral to the electric circuit of the heart.

tDCS might be confounded by tsDCS (Picelli *et al.*, 2015), outcomes did not measure walking ability or mobility (Khedr *et al.*, 2013; Montenegro *et al.*, 2016) and lack of precise data for analysis (Danzl *et al.*, 2013). In contrast, current analysis included five additional studies published between 2017 and 2018 and provided the most up-to-date synthesis of the evidence (12 studies, n = 248). Besides, instead of pooling all related measures (TUG, Tinetti test, and FAC) into a common category of mobility (Li *et al.*, 2018), the current study extracted and examined the effects of each mobility measurements. Essentially, analyses revealed that the effect size for Tinetti test (SMD = 0.441), walking speed (SMD = 0.195), and walking endurance (SMD = 0.209) were all relatively small and non-significant (Cohen, 1988).

The reason accounting for the small effect size on Tinetti test may be that the scale reflects more on balance ability than gait or walking performance. Tinetti test comprises of a balance subscale (POMA-B) and a gait subscale (POMA-G). The balance score of Tinetti test (16/28) takes more weight than the gait score (12/28) (Canbek *et al.*, 2013). Therefore, Tinetti test may reflect a patient's balance ability better than patient's gait or walking ability. Furthermore, according to the previous meta-analyses and our result, tDCS seemed to be less effective on improving balance function after stroke (Li *et al.*, 2018; Kang *et al.*, 2020). Therefore, we speculated that balance ability which depends on the integrated actions of multiple systems may be difficult to be improved by tDCS alone. The same rationale might account for the non-significant findings on gait speed and walking endurance (6MWT) as well. Balance ability as measured by BBS has been identified as the strongest predictor for both 10 m and 6 minutes walking in stroke patients (Patterson *et al.*, 2007). Therefore, when the tDCS could not effectively improve balance ability, the capability to improve walking speed and walking endurance may also be limited.

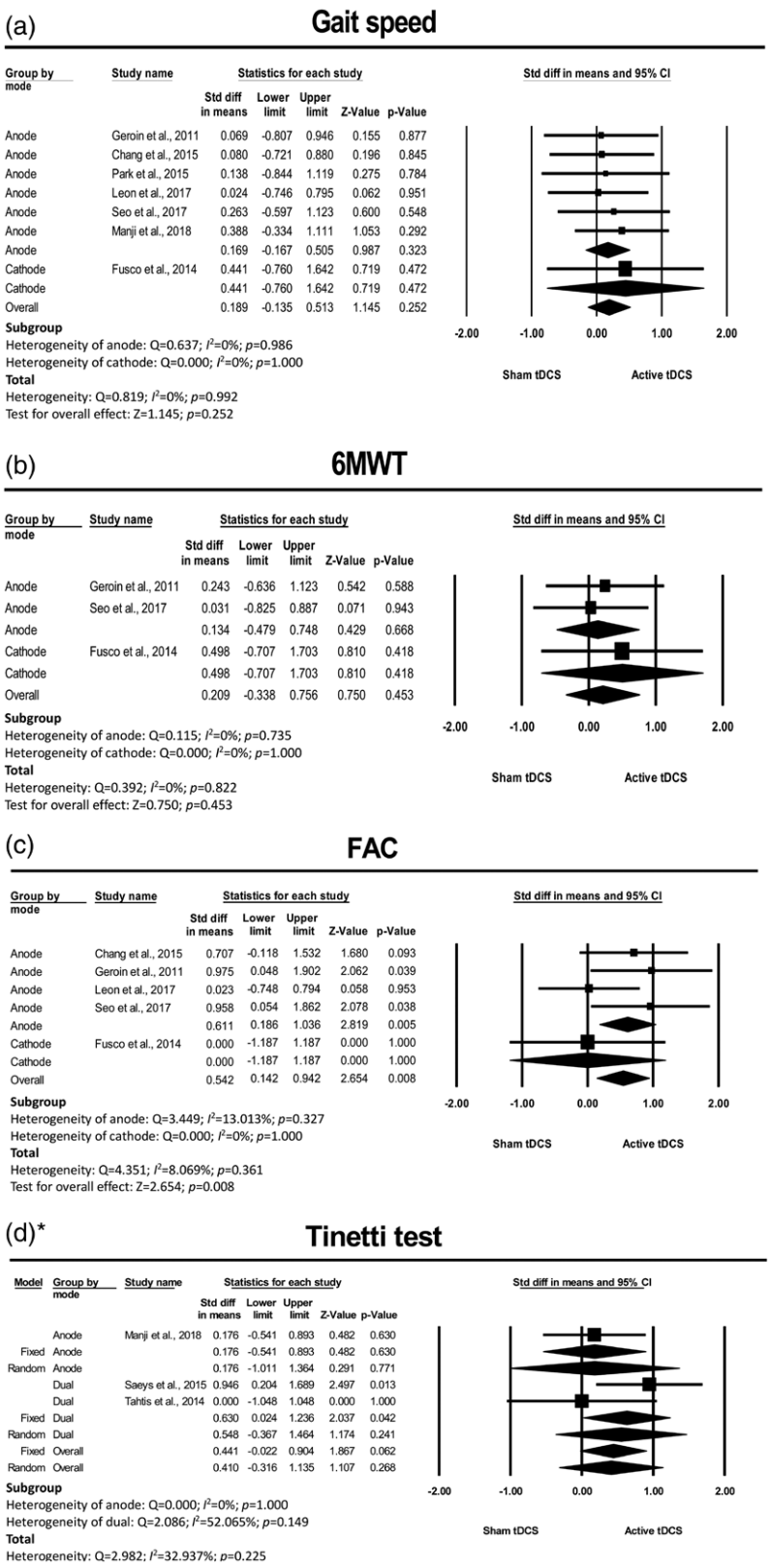
In subgroup analyses, we found positive effects of the unilateral anodal tDCS on FAC (trials = 4) and dual-hemispheric tDCS on TUG (trials = 2). To the best of our knowledge, these positive effects were revealed for the first time in the literature. From the analysis on FAC, when the effect of cathodal tDCS was removed, the effect of anodal tDCS remained significant with larger effect size (Fig. 2c). Notably, dual-hemispheric tDCS not only exerted a larger effect size than unilateral anodal tDCS but also was the only significant finding in the subgroup analyses on TUG (Fig. 2f). Previous study has demonstrated that dual-hemispheric tDCS could increase excitability in the ipsilesional hemisphere, reduce cortical excitability in the contralesional hemisphere and reduce the transcallosal inhibition from the contralesional hemisphere simultaneously in stroke patients (Bolognini *et al.*, 2011). Therefore, dual-hemispheric tDCS has been expected to improve gait or motor performance of lower

Table 2 Characteristics of included studies

Study ID	Study design	Total, N (tDCS/ Sham)	Age (tDCS/Sham)	Stroke duration (tDCS/Sham)	Stroke type, tDCS(I/H)	Stroke type, sham(I/H)	Affected hemisphere (tDCS/Sham)	Additional treatment	Adverse effect	Follow up
Geroin *et al.* (2011)	RCT	20 (10/10)	63.6 ± 6.7/63.3 ± 6.4	25.7 ± 6.0/26.7 ± 5.1 (m/o)	10/0	10/0	–	RAGT	No harm	After 2 weeks
Danzl *et al.* (2013)	RCT	8 (4/4)	64.8 ± 14.9/70.8 ± 11.1	4.8 ± 4.5/3.2 ± 2.7 (m/o)	2/2	4/0	4L/4L	RGO	No harm	After one month
Cha *et al.* (2014)	RCT	20 (10/10)	59.8 ± 11.4/57.8 ± 9.9	13.8 ± 4.6/14.5 ± 3.6 (m/o)	–	–	4R 6L/5R 5L	–	–	–
Fusco *et al.* (2014)	RCT	11 (5/6)	56.4 ± 17.2/60.0 ± 8.1	19.01 ± 8.0 (days)	11/0		3R 2L/2R 4L	–	–	After 10 days (1 month and discharge
Tahtis *et al.* (2014)	RCT	14 (7/7)	67.3 ± 11.8/56.4 ± 12.3	19.7 ± 5.2/25.3 ± 10.9 (days)	7/0	7/0	4R 3L/4R 3L	–	No harm	–
Chang *et al.* (2015)	RCT	24 (12/12)	59.9 ± 10.2/65.8 ± 10.6	16.0 ± 6.2/16.6 ± 5.2 (days)	12/0	12/0	6R 6L/7R 5L	–	–	–
Park *et al.* (2015)	RCT	16 (8/8)	59.0 ± 6.0/57.7 ± 10.0	23.8 ± 16.2/22.5 ± 14.5 (m/o)	4/4	5/3	3R 5L/4R 4L	TRT	–	–
Saeys *et al.* (2015)	RCT cross-over design	31 (16/15)	62.00 ± 9.61/64.53 ± 7.23	45.5 ± 21.8/38.4 ± 15.1 (days)	26/5		14R 17L	–	No harm	–
van Asseldonk and Boonstra (2016)	RCT cross-over design	10	58.0 ± 11.7	44.7 ± 37.7 (m/o)	8/2		4R 6L	–	–	After 15 and 45 mins
Leon *et al.* (2017)	Active-control	32 (9/23)	49 ± 9/49 ± 11	53 ± 25/64 ± 33 (days)	6/3	13/10	33.3%R/52.2%R	RAGT	+[2]	–
Seo *et al.* (2017)	RCT	21 (11/10)	62.9 ± 8.9/61.1 ± 8.9	152.5 ± 122.8 /75.5 ± 83.4 (m/o)	7/3	9/2	8R 2L/5R 6L	RAGT	–	After 4 weeks
Klomjai *et al.* (2018)	RCT cross-over design	19 (10/9)	57.2 ± 2.8	3.2 ± 0.4 (m/o)	19/0		7R 12L	–	+[1]	–
Manji *et al.* (2018)	RCT cross-over design	30 (15/15)	62.2 ± 10.1/63.7 ± 11.0	134.5 ± 55.7 /149.7 ± 24.2 (days)	9/6	8/7	–	BWSTT	–	–
Utarapichat and Kitisomprayoonkul (2018)	RCT cross-over design	10 (5/5)	57.1 ± 12.2	34.1 ± 18.9 (m/o)	10/0		5R 5L	–	No harm	–

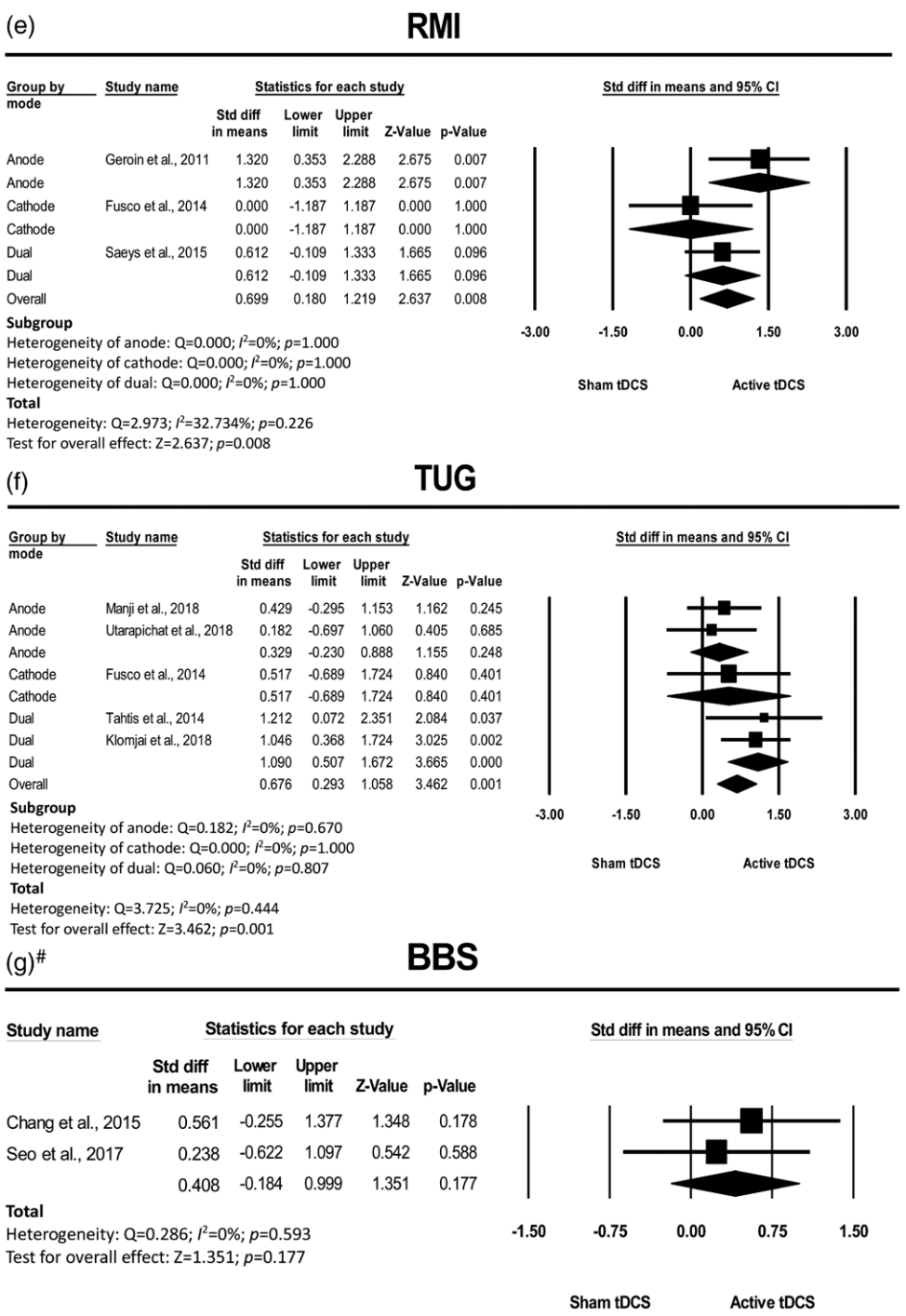
–, not reported; +[1], Mild headache after tDCS; +[2], Mild headache during and after tDCS, slight itching; BWSTT, body weight-supported treadmill; H, hemorrhage; I, ischemic; L, left; m/o, month after onset; mins, minutes; R, right; RAGT, robot-assisted gait training; RCT, randomized controlled trial; RGO, robotic gait orthosis; TRT, task-related training.

Fig. 2



(*Continued*)

Fig. 2 (continued)



Forest plots for primary and secondary outcomes with subgroup analyses of mode application (a) gait speed, (b) six-minute walking test, (c) functional ambulation category, (d) Tinetti test, (e) Rivermead Mobility Index, (f) timed up and go test, (g) Berg Balance Scale. CI, confidence interval; Std diff in means, standard difference in means. *Anode tDCS used the fixed-effect model while dual-hemispheric tDCS used the random effect model. #Data without subgroup analysis.

extremity in stroke patients better than unilateral tDCS (van Asseldonk and Boonstra, 2016). From our review and subgroup analyses, four studies have examined the effects of dual-hemispheric tDCS on gait-related outcomes after stroke. However, due to unavailable of research data (van Asseldonk and Boonstra, 2016) and limited outcomes adopted by studies, only the effects on TUG and Tinetti test could be extracted. In

contrast, dual-hemispheric tDCS not only significantly improved TUG but also exerted larger effect size (SMD = 1.090) than anodal tDCS. It is of interest to know that Klomjai *et al.* (2018) did not find a significant effect of dual-hemispheric-tDCS on TUG (P = 0.883). However, with statistical synthesis of two studies, the effect of dual-hemispheric tDCS on TUG became evident (Tahtis *et al.*, 2014; Klomjai *et al.*, 2018). In addition, a strong negative association had been identified between TUG score and the maximal torque generated by gastrocnemius (r = −0.86) in people with chronic stroke (Ng and Hui-Chan, 2005). Thus, when tDCS was found to effectively improve muscle strength of lower limb in stroke patients (Li *et al.*, 2018), performance of TUG may be enhanced by tDCS as well. Based on these findings, current results support in part that dual-hemispheric tDCS may have its unique contribution in promoting walking ability in stroke patients. Finally, in the included studies, only Fusco *et al.* (2014) have examined the effect of cathodal tDCS on gait and walking-related performances after stroke. Therefore, none of effects could be extracted for cathodal tDCS from our analysis.

This systematic review and meta-analysis provides up-to-date evidences on the effects of tDCS. However, the results should be interpreted with caution under following limitations. First, studies published in languages other than English and Chinese were not included. Second, two of the included studies did not provide the data for quantitative evidence synthesis. Third, to extract the effects for each outcome related to walking ability and different modes of tDCS, the subgroup analyses were limited by the small trial number. Fourth, some of the included studies explored the immediate effects of tDCS with only one session of treatment (Tahtis *et al.*, 2014; van Asseldonk and Boonstra, 2016; Klomjai *et al.*, 2018; Utarapichat and Kitisomprayoonkul, 2018), effects revealed by current study may be contributed by single as well as multiple sessions of tDCS. Finally, the publication bias should be considered as a positive result and future research should be more representative.

Conclusion

In conclusion, this meta-analysis suggests that tDCS improves walking ability with an exception of walking speed and endurance in patients with stroke. Both anodal and dual-hemispheric tDCS exert positive effects on promoting walking-related performances after stroke. However, difficulty in improving balance performance by tDCS may limit the effects of tDCS on walking speed and/or walking endurance.

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Conflicts of interest

There are no conflicts of interest.

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