Backward locomotor treadmill training combined with transcutaneous spinal direct current stimulation in stroke: a randomized pilot feasibility and safety study

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BRAIN COMMUNICATIONS

Backward locomotor treadmill training combined with transcutaneous spinal direct current stimulation in stroke: a randomized pilot feasibility and safety study

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Walking impairment impacts nearly 66% of stroke survivors and is a rising cause of morbidity worldwide. Despite conventional post-stroke rehabilitative care, the majority of stroke survivors experience continued limitations in their walking speed, temporospatial dynamics and walking capacity. Hence, novel and comprehensive approaches are needed to improve the trajectory of walking recovery in stroke survivors. Herein, we test the safety, feasibility and preliminary efficacy of two approaches for post-stroke walking recovery: backward locomotor treadmill training and transcutaneous spinal direct current stimulation. In this double-blinded study, 30 chronic stroke survivors (>6 months post-stroke) with mild-severe residual walking impairment underwent six 30-min sessions (three sessions/week) of backward locomotor treadmill training, with concurrent anodal ($N = 19$) or sham transcutaneous spinal direct current stimulation ($N = 11$) over the thoracolumbar spine, in a 2:1 stratified randomized fashion. The primary outcomes were: per cent participant completion, safety and tolerability of these two approaches. In addition, we collected data on training-related changes in overground walking speed, cadence, stride length (baseline, daily, 24-h post-intervention, 2 weeks post-intervention) and walking capacity (baseline, 24-h post-intervention, 2 weeks post-intervention), as secondary exploratory aims testing the preliminary efficacy of these interventions. Eighty-seven per cent ($N = 26$) of randomized participants completed the study protocol. The majority of the study attrition involved participants with severe baseline walking impairment. There were no serious adverse events in either the backward locomotor treadmill training or transcutaneous spinal direct current stimulation approaches. Also, both groups experienced a clinically meaningful improvement in walking speed immediately post-intervention that persisted at the 2-week follow-up. However, in contrast to our working hypothesis, anodal-transcutaneous spinal direct current stimulation did not enhance the degree of improvement in walking speed and capacity, relative to backward locomotor treadmill training + sham, in our sample. Backward locomotor treadmill training and transcutaneous spinal direct current stimulation are safe and feasible approaches for walking recovery in chronic stroke survivors. Definitive efficacy studies are needed to validate our findings on backward locomotor treadmill training-related changes in walking performance. The results raise interesting questions about mechanisms of locomotor learning in stroke, and well-powered transcutaneous spinal direct current stimulation dosing studies are needed to understand better its potential role as a neuromodulatory adjunct for walking rehabilitation.

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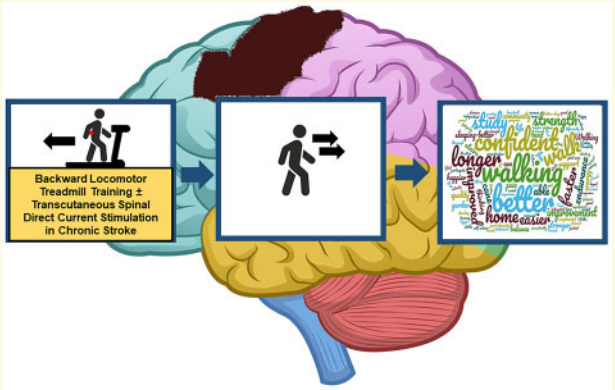
Abbreviations: 6MWT = 6-min walk test; 10MWT = 10-m walk test; BLTT = backward locomotion treadmill training; PHQ9 = Patient Health Questionnaire; TsDCS = transcutaneous spinal direct current stimulation

Graphical Abstract



Introduction

Walking impairment after a stroke is primarily due to the loss of adequate lower extremity function and is a significant cause of disability, with nearly two-thirds of stroke survivors having significant limitations in walking (Dobkin, 2005). This impairment results in an increased risk for falls, fractures and a progressive decline in mobility (Duncan *et al.*, 2011; Langhorne *et al.*, 2011). With the increasing survival rate after stroke, walking impairment is becoming an even greater public health issue. Hence, novel neurorehabilitative approaches are needed to improve the potential and trajectory of walking recovery after stroke. This study explores non-body weight supported backward locomotion treadmill training (BLTT) as a novel rehabilitation approach, and investigates transcutaneous spinal direct current stimulation (tsDCS) as an adjunct for walking rehabilitation in stroke.

Backward walking

The network control of forward and backward walking in humans remains an area of high interest. While the precise relationship of these networks is not fully understood (Winter *et al.*, 1989; Choi and Bastian, 2007; Jansen *et al.*, 2012; Musienko *et al.*, 2012; Hoogkamer *et al.*, 2014), recent physiologic and rehabilitation studies suggest that forward and backward locomotor networks, while independent, may interact such that backward training could improve performance with forward locomotion (Yang *et al.*, 2005; Hao and Chen, 2011; Michaelsen *et al.*, 2014; El-Basatiny and Abdel-Aziem, 2015; Foster *et al.*, 2016; Rose *et al.*, 2018). For example, kinematic studies, performed in neurologically intact individuals, suggest that backward walking training improves forward walking ability to a greater extent than forward walking training alone, because backward walking training incorporates supplementary core and lower extremity muscle groups which are less active during forward walking (Winter *et al.*, 1989; Grasso *et al.*, 1998; Błażkiewicz, 2013). Also, backward walking has been suggested to improve walking symmetry by targeting the maladaptive flexor-synergy gait pattern associated with central nervous system injury (Thorstensson, 1986; Winter *et al.*, 1989; Duysens *et al.*, 2013; Rose *et al.*, 2018). Since backward walking relies more heavily on proprioception and sensorineural integration, to know where the foot is in space, backwards training could also theoretically improve walking stability and balance over time (Hao and Chen, 2011; Fritz *et al.*, 2013; Ordway *et al.*, 2016; Rose *et al.*, 2018).

Backward locomotion treadmill training

Our training approach in this study differs from typical overground backward walking because the entirety of the training is performed on a non-body weight supported treadmill which facilitates high repetition of practice while enabling real-time control of training speed. Moreover, the absence of body weight support provides even a greater challenge because it forces participants to

bear more weight on their paretic limb (Wernig and Wernig, 2010). In addition, the presence of sensors underneath the belt enables for collection of temporospatial data comparable over sessions (Yeon-Gyu and Jung-Wan, 2016; Zachary *et al.*, 2017).

Past studies have demonstrated that BLTT is feasible in young, and neurologically intact adults; however, its safety and feasibility have not been tested in chronic stroke survivors. A few physiological considerations could make BLTT particularly challenging in this population. For example, stroke commonly impacts chronologically older individuals, which is associated with a decline in gait speed, joint range of motion and spatiotemporal ability (Stacy *et al.*, 2007). Moreover, functional neuroimaging studies have reported an increased tendency for prefrontal compensatory recruitment during normal walking in this population (Kurz *et al.*, 2012; Chatterjee *et al.*, 2019). In addition, backward walking is characteristically more physically demanding than walking forward (Flynn *et al.*, 1994; Terblanche *et al.*, 2005) and requires movement patterns that tend to be particularly difficult after stroke (i.e. knee flexion and ankle dorsiflexion with hip extension) (Nilsson *et al.*, 2001). Hence, it is possible that BLTT may be too cerebrally and physically demanding for chronic stroke survivors to complete. Therefore, the primary objective of this study was to investigate the safety and feasibility of BLTT, while in parallel obtaining preliminary outcome data for training-related effects BLTT on overground walking in the chronic stroke population.

Direct current stimulation

The secondary objective of this study was to explore if the concurrent application of a direct current stimulation over the thoracolumbar region of the spinal cord could enhance training-related changes.

Over the last 25 years, direct current stimulation has gained traction as a promising non-invasive neuromodulatory tool for stroke neurorehabilitation (Stagg *et al.*, 2009; Schlaug and Cohen, 2010; Kang *et al.*, 2016). Early studies in the young, elderly, and stroke populations have suggested that its application over the scalp (tDCS), for multiple sessions, may enhance the effects of training by facilitating the acquisition rate and retention of the learned task (Reis *et al.*, 2009; Antal *et al.*, 2010; Fritsch *et al.*, 2010; Kadosh *et al.*, 2010; Dayan *et al.*, 2013; Snowball *et al.*, 2013). However, reports on the effect of tDCS with lower extremity or locomotor training have been less encouraging (Madhavan and Stinear, 2010; Geroin *et al.*, 2011; Geiger *et al.*, 2017). Some have suggested that the inefficacy of tDCS to modulate lower extremity and walking recovery may be a result of the inefficient distribution of direct current to reach critical regions involved in human locomotion, such as the lower extremity region of the motor cortex, subcortical locomotor regions and spinal cord (Jeffery *et al.*, 2007; Jones *et al.*, 2016). Hence, an alternative approach to modulate the central locomotor network termed 'transcutaneous spinal direct current stimulation (tsDCS)' has been suggested (Priori *et al.*, 2014).

Supported by electrical current modelling (Parazzini *et al.*, 2014; Fregni *et al.*, 2015; Fiocchi *et al.*, 2016; Kuck *et al.*, 2017), preclinical (Zaghloul, 2014, 2016; Weiguo *et al.*, 2015), neurophysiologic (Cogiamanian *et al.*, 2012; Priori *et al.*, 2014) and neuroimaging studies (Schweizer *et al.*, 2017), a growing body of literature suggests that tsDCS can modulate activity at multiple levels of the central nervous system, including the segmental spinal cord (Winkler *et al.*, 2010; Lamy *et al.*, 2012; Hubli *et al.*, 2013), ascending lemniscal and nociceptive pathways (Cogiamanian *et al.*, 2008; Cogiamanian *et al.*, 2011; Truini *et al.*, 2011), as well as cortical regions (Bocci *et al.*, 2014, 2015*a*, *b*, *c*; Marangolo *et al.*, 2017; Schweizer *et al.*, 2017). In addition, a recent proof-of-concept study from our group, in young and neurologically intact individuals, found that anodal tsDCS applied over the lower thoracic region (T-11) concurrently with BLTT, increased the acquisition rate and retention of backward walking speed up to 2 weeks post-training (Awosika *et al.*, 2019). Therefore, this study explores if tsDCS could comparably enhance the effect of BLTT on forward walking in chronic stroke survivors.

Based on the completion rates of past stroke recovery trials from our group (Kluding *et al.*, 2013; Boyne *et al.*, 2016; Harvey *et al.*, 2018), we anticipated that 30 patients could be enrolled and randomized within 24 months, and predicted that greater than 70% of those participants would complete the study. In line with past neuromodulation studies using direct current stimulation (Antal *et al.*, 2017), we anticipated that tsDCS would be well-tolerated. Lastly, while this study was not powered to detect a significance between the two groups (BLTT + sham tsDCS vs. BLTT + anodal tsDCS), we hypothesized that anodal tsDCS would demonstrate a trend towards greater improved walking performance.

Materials and methods

Participants

This study was conducted at the University of Cincinnati Neurorecovery Lab from 5 September 2017, to 4 February 2019. Community-dwelling individuals between 18 and 80 years of age, with mild to severe gait impairment due to chronic stroke (>6 months), either ischaemic or haemorrhagic were recruited for this study. Prior to group randomization, study participants had to demonstrate the ability to: provide consent (Mini-Mental State Exam Score >23), ambulate without a walker and maintain ≥0.13 m/s speed on the treadmill while walking backwards for 6 min. They were additionally asked to abstain from both formal physiotherapy and botulinum

Table 1 Baseline demographic and gait variables per intervention group

	BLTT + sham tsDCS ($n = 11$)	BLTT + anodal tsDCS ($n = 19$)	*P*-value
Demographic variables			
Age (years)	54.74 ± 10.9	58.55 ± 7.61	0.269
Stroke age (months)	62.25 ± 72.0	62.22 ± 66.3	0.999
Gender			
Male	6 (55%)	10 (53%)	0.917
Female	5 (45%)	9 (47%)	
Hemiplegic side			
Right	7 (64%)	11 (58%)	0.750
Left	4 (36%)	8 (42%)	
Stroke type			
Ischaemic	9 (82%)	15 (79%)	0.845
Haemorrhagic	2 (18%)	4 (21%)	
Behavioural-Cognitive Scales			
Patient Health Questionnaire (PHQ9)	3.909 ± 4.53	3.053 ± 2.93	0.534
Mini-Mental Status Exam	28.27 ± 1.85	27.88 ± 2.87	0.690
Gait variables			
10-m walking speed (*fast*)-m/s	1.105 ± 0.31	0.982 ± 0.53	0.490
Cadence (steps/min)	124.2 ± 26.9	104.9 ± 31.6	0.101
Stride length (cm)	118.8 ± 25.5	118.9 ± 44.0	0.995
Gait impairment severity			
Mild	3 (27%)	4 (21%)	0.712
Moderate	7 (64%)	10 (53%)	0.564
Severe	1 (9%)	5 (26%)	0.268

toxin treatments at least 2 weeks prior to enrolment and for the duration of training and follow-up. The exclusion criteria ruled-out individuals with an unstable cardiopulmonary status which may preclude participation in a moderate-high intensity exercise programme, severe lower extremity spasticity (modified Ashworth >2/4), significant language barrier which might prevent the participant from following instructions during training and testing, and untreated depression [>10 on the Patient Health Questionnaire (PHQ9)].

Study design

Potential study participants were screened until the enrolment goal of 30 randomized participants was reached. Participants meeting the inclusion and exclusion criteria were randomized in a 1:2 stratified fashion to either sham ($N = 11$) or anodal tsDCS ($N = 19$), respectively—based on baseline 10-m walk test (10MWT) speed, prior to BLTT initiation, on Day 2 (D2) of the study (Table 1). This stratification ratio was used to maximize the number of participants receiving anodal tsDCS, in an effort to reduce the variance in the estimated treatment effect. Group allotment was performed by an independent research coordinator, removed from training and outcomes testing. In addition, the patient, therapists and outcome assessors were blinded to the group allocation.

Impairment classification

To determine the impact of baseline walking impairment level on BLTT completion and outcome, participants were categorized into mild, moderate or severe walking impairment using the self-selected 10MWT (*self-selected*) at screening (D1), where ≥0.8–1.2 m/s was classified as mild, ≥0.4 to <0.8 m/s as moderate and <0.4 m/s as severe (Perry *et al.*, 1995).

Intervention

Backward locomotion treadmill training

Screening (D1). All study participants underwent 6 min of BLTT on screening day (D1) for orientation and to screen out individuals who were not able to achieve ≥0.13 m/s on the treadmill—the minimum belt speed needed to demonstrate adequate neuromotor capacity for participating in aerobic training (Macko *et al.*, 2005; Ivey *et al.*, 2008). For safety, participants were connected to a non-body weight supported safety harness, with their backs facing the head of the treadmill (Fig. 1A). Participants were permitted to hold-on to one handrail for support. The belt speed was started at slowest possible speed (≥0.04 m/s) and increased, based on the participant's level of comfort, during the 6 min (Supplementary Table 1). A physical therapist remained next to the participant's paretic side to provide assistance during backward leg extension, as needed. A second therapist was available during unique instances when a participant needed assistance on the non-paretic side (Supplementary Table 2).

Training (D2–D7). Participants who completed the ≥0.13 m/s inclusion threshold advanced to the first day of training (D2) (Fig. 1B). The training consisted of four 6-min blocks. The self-selected treadmill speed, established on D1, was used as the starting speed on the first block of D2. Likewise, for D3–D7, the training treadmill speed

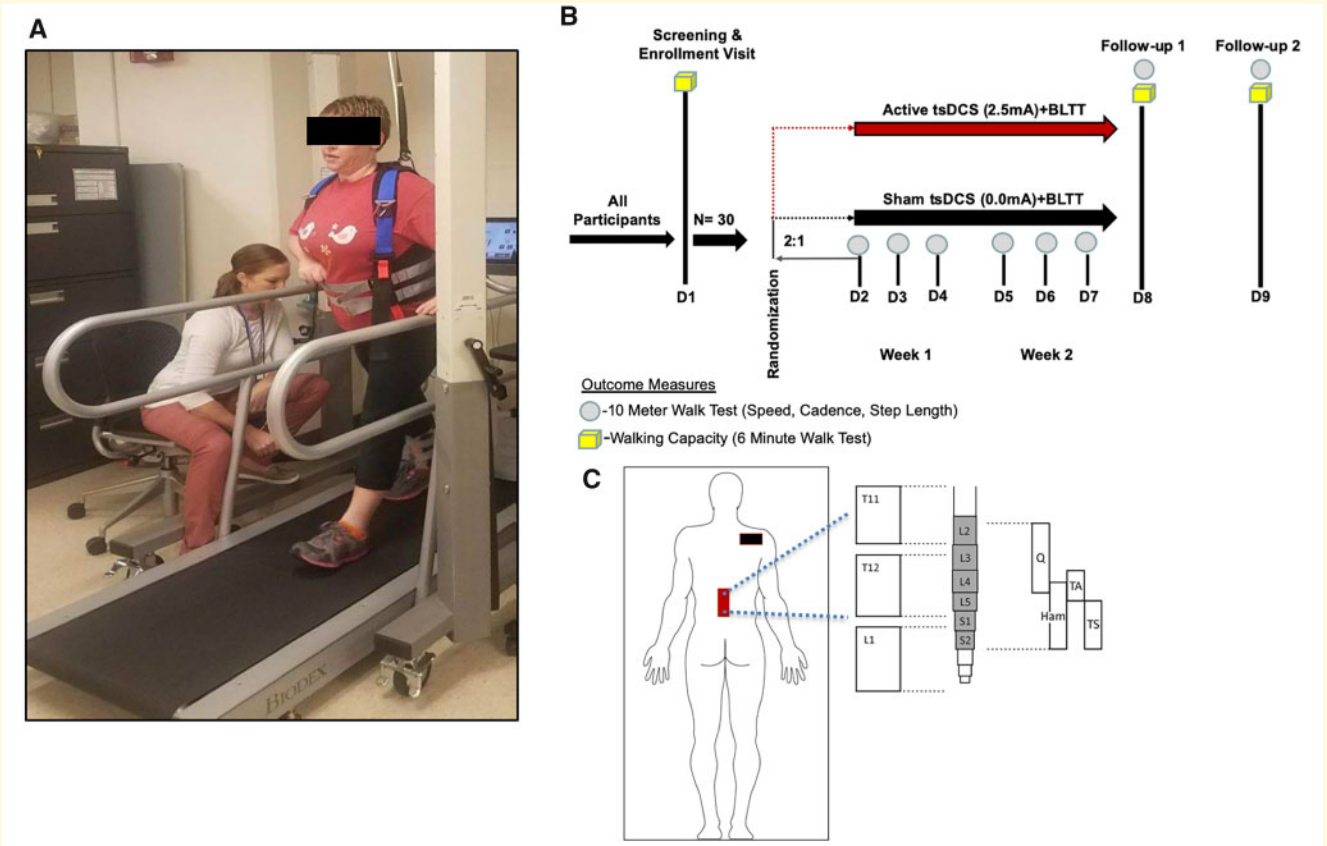


Figure 1 Training schematic. Study participants underwent six (D2–D7), 30-min sessions of non-bodyweight supported BLTT, with concurrent sham or anodal tsDCS, applied over T-11/12 (red rectangle) and cathode electrode placed over the right shoulder (black rectangle).

used on the fourth block of the preceding day was used as the starting speed for the subsequent session. In communication with the participant, the therapist continuously adjusted the speed to maintain a sustainable challenge. To reduce fatigue, all participants received 2-min seated rest breaks between each of the 4, 6-min training blocks, totalling ~30 min. Six of the 30 study participants needed physical assistance over the 6 days of training (minimal to maximal). For safety and to ensure adequate effort (at least 50% of the predicted maximal heart rate), a Polar H7 (POLAR®, USA) heart rate monitor was worn at all times during training (see Supplementary Table 3). Participants were also offered chocolate milk after training to reduce training-associated muscle soreness (Pritchett and Pritchett, 2012).

Transcutaneous spinal direct current stimulation

TsDCS (2.5 mA, 30 min) was delivered, during BLTT, from a battery-driven programmable direct current stimulator (Soterix, USA) connected to surface electrodes (saline-soaked synthetic sponge of 7×5 cm, and 0.6 cm depth). Prior to the initiation of training, the anode/sham electrode was centred on the T-11 spinous process of the thoracic spine with the major axis parallel to the spinal cord, a second electrode was placed over the right shoulder, aligned with previous studies demonstrating modulation of segmental spinal reflex excitability with this montage (Vergari *et al.*, 2008; Truini *et al.*, 2011; Lamy *et al.*, 2012). The second electrode was placed over the right shoulder (Fig. 1C). A tsDCS lumbar body strap (Soterix, USA) was used to secure electrode positioning in place. Computerized modelling of this electrode montage and stimulation parameters estimates a current density of 0.071 mA/cm^2, delivering a total charge density of 85.7 mC/cm^2 (Cogiamanian *et al.*, 2008), which is well within safety levels. The direct current stimulator was programmed to ramp up current to 2.5 mA over a 30-s period and similarly ramped down at the end of the stimulation. Sham tsDCS was achieved by delivering a 2.5-mA current over a period of 30 s at the beginning and end of the stimulation period.

Outcomes measures

Safety, feasibility and tolerability

A tolerability, activity and safety questionnaire (Supplementary Fig. 1) was completed by the patient at the first post-training follow-up (D8). Information regarding study enrolment, attrition and adverse events were documented throughout the study. The primary outcome was the proportion of participants who completed the BLTT study. Completion was defined as finishing the

entirety of the training protocol (180 min) and returning for the two follow-up visit days [24-h post-training Day 6 (D8), and 2-week post-training Day 6 (D9)].

10-m walk test

Community ambulation is correlated with gait speed (Perry *et al.*, 1995), and changes in gait speed that result in a transition to a higher category of ambulation classification are associated with improved function and quality of life. Therefore, 10MWT is the gold standard measure of post-stroke walking function that reflects overall mobility (Lord *et al.*, 2004; Schmid *et al.*, 2007) and health status (Studenski *et al.*, 2003). Training-related changes in gait speed were assessed with the 10MWT. This test was administered at screening, before each BLTT session (D2–D7), and at follow-up (D8–D9). Participants were instructed to walk as fast as possible, with or without an assistive device (single pint cane or quad cane), with three attempts. The fastest of the three trials was used in the analysis. To limit the influence of D1 orientation training-effect on outcomes, the 10MWT speed for D2 was set as the baseline.

Gait dynamics

Temporal (cadence) and spatial dynamics (Δ stride length) were acquired using the Zeno Walkway gait analysis mat (Protokinetics, PA, USA) during the10MWT. These data were captured and recorded with the Protokinetics Movement Analysis Software and later exported for offline analysis.

Walking capacity

Walking capacity, as determined by performance on the 6-min walk test (6MWT), is the most influential individual predictor of limited versus full community ambulation (Fulk *et al.*, 2017). Participants were instructed to walk as fast as possible back and forth in a 23-m corridor, with or without an assistive device (single-point cane or quad cane) for 6 min. The total distance travelled was measured and documented by the blinded therapist after the test. The 6MWT was administered at screening, D8 follow-up (~24 h following the sixth day of training), and D9 (2-week post-training).

Statistical analysis

The enrolment goal of 30 was determined based on the site recruitment rate from past protocols from our group. Normality assumption was tested by the Shapiro–Wilk method, and the significance level was set at $P = 0.05$ for all measures. Between-group differences in the proportion who completed the study and tolerability outcomes were determined using the Chi-squared test. Linear mixed-effects models were used to test for within-group change and between-group differences in change for gait speed, cadence and stride length (Δ = D8–D2), and for walking capacity (Δ = D8–D1). These models included each gait measure (separately) as the dependent variable, with fixed effects for time point, group and their interaction and a random effect for participant, to account for the correlated nature of repeated measures from the same person. Also, to account for the relative imbalance of participants with severe walking impairment in the anodal versus sham groups, we performed a secondary analysis adjusting for baseline gait speed. The retention of effect within- and between-groups on each walking measure was determined by comparing the change between D9 and D8. Since walking outcomes were exploratory, adjustment for multiple comparisons was not performed. Walking data from one participant, in the control group, were excluded at 5-timepoints (D5–D9) for 10MWT, and 6MWT (D8, D9), due to interspersed periods of 'walk-jogging', characterized by absence of double support time during walking trials on the gait analysis mat.

Data availability

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Results

Feasibility

From 5 September 2017, to 7 January 2019, 37 chronic stroke survivors with residual walking impairment were enrolled, with 30 randomized (Fig. 2). There were no significant baseline differences, in age, behavioural-cognitive scales, stroke type, or severity, or gait metrics, between groups (Table 1).

Completion rate

Twenty-six of the 30 (87%) randomized participants completed the study (Fig. 2). All seven randomized participants (100%) with mild walking impairment completed the study, irrespective of group allocation. Sixteen of 17 (94%) of participants with moderate walking impairment completed the study. The dropout from this cohort was in the anodal-tsDCS group and discontinued due to a viral gastrointestinal illness. Three out of six (50%) of participants with severe walking impairment completed the study. There was one dropout in the sham group, on D9, due to a family illness. There were two dropouts in the anodal tsDCS group: one participant discontinued the study on D2 due to the development of leg and back spasms during block 1 of training, and the second did not meet treatment fidelity to satisfy the 'completion' criteria on D3 and D6, due to fatigue and transient acute on chronic arthritic knee pain.

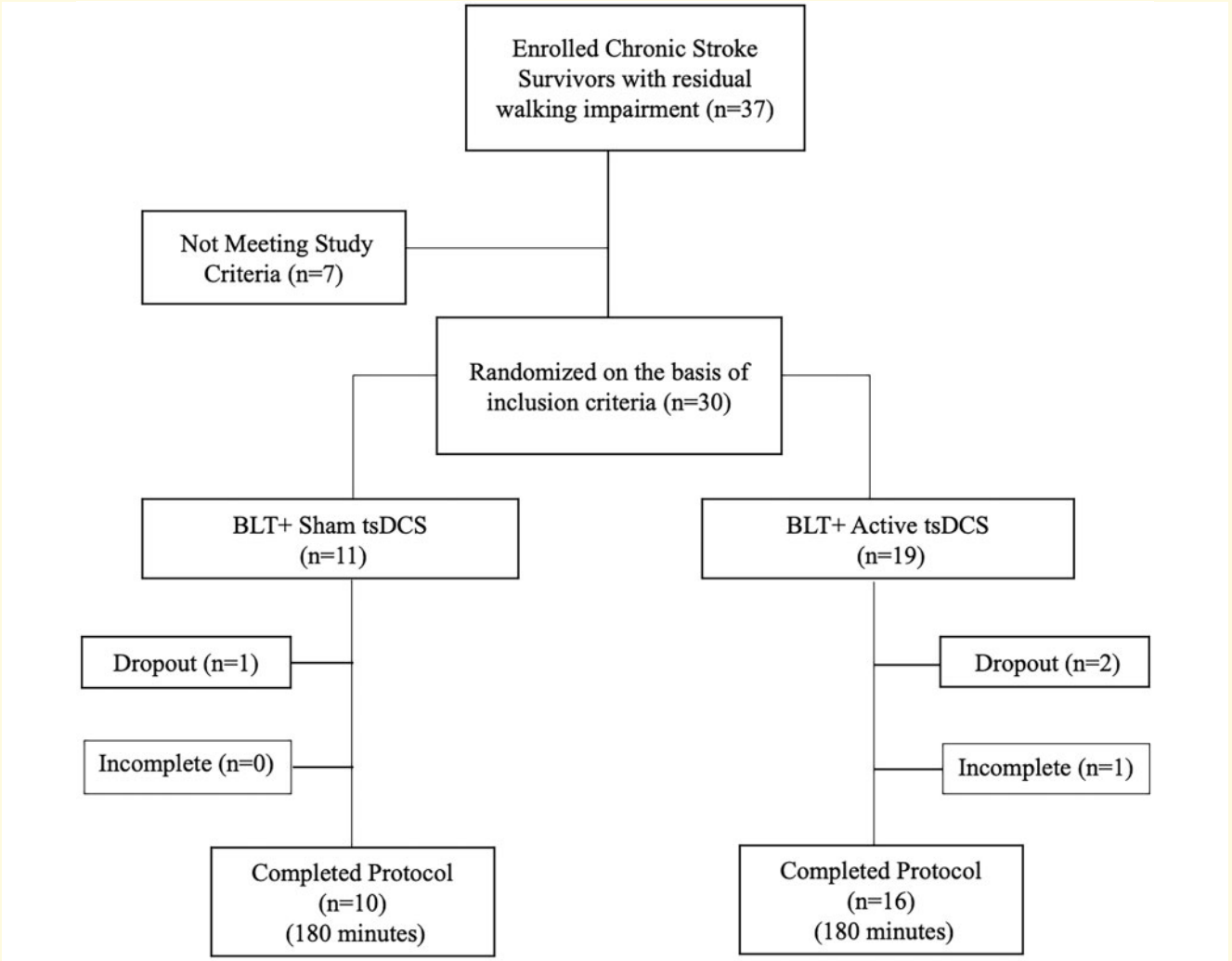


Figure 2 Flow diagram of the study.

Tolerability, activity and safety questionnaire

BLTT was well tolerated by participants in both groups (anodal tsDCS and sham tsDCS). Participants from both groups reported similar improvements in activity level ($P = 0.152$), strength ($P = 0.188$), energy level ($P = 0.370$) and mood ($P = 0.238$). On a 0–10 scale, both groups similarly scored <1, for headache ($P = 0.207$), neck pain ($P = 0.449$) or pain ($P = 0.290$), tingling ($P = 0.423$), itching ($P = 0.280$), burning ($P = 1.000$) or electric shock sensation ($P = 0.754$) related to tsDCS. Reports of soreness or fatigue were minimal and similar between groups, $P = 0.086$, $P = 0.472$, respectively (Table 2).

Serious adverse events

There were no serious adverse events in the study, including cardiac, cerebrovascular, orthopaedic injuries (i.e. fracture or dislocation) or incidences requiring a visit to the emergency room, hospitalization, persistent or significant incapacity, or death.

Secondary outcome measures

Overground walking speed

Both groups demonstrated a significant improvement in overground walking speed on the 10MWT after BLTT ($P < 0.001$), and reached minimal clinically importance difference (MCID = 0.16 m/s) in speed for stroke walking recovery [mean (95% CI): 0.412 m/s (0.213–0.611), sham, 0.215 m/s (0.119, 0.310), anodal], (Schmid *et al.*, 2007). Participants receiving sham tsDCS demonstrated a greater improvement in walking speed (D2–D8), relative to the anodal tsDCS ($P = 0.016$). This result was still similar, although just non-significant, after adjusting for baseline differences in walking speed ($P = 0.054$) (Fig. 3B). There was retention in walking speed up to 2 weeks following the period of training in both groups;

Table 2 Safety and tolerability questionnaire

Questions[a]			
	Sham tsDCS + BLTT	**Anodal tsDCS + BLTT**	***P*-value**
Areas of improvement			
• Activity level	6.818 ± 3.46 (median: 8)	4.889 ± 3.39 (median: 5)	0.152
• Strength	6.727 ± 3.04 (median: 7)	5.111 ± 3.18 (median: 5)	0.188
• Energy level	6.454 ± 3.33 (median: 7)	4.611 ± 3.03 (median: 5)	0.137
• Mood	6.545 ± 3.11 (median: 7)	4.833 ± 4.02 (median: 5.5)	0.238
Symptom questions not specific to one intervention			
• Headache	0.455 ± 1.51 (median: 0)	0.000 ± 0.00 (median: 0)	0.207
• Neck pain	0.000 ± 0.00 (median: 0)	0.056 ± 0.24 (median: 0)	0.449
Symptom severity questions related to BLTT			
• Soreness	1.818 ± 1.72 (median: 2)	0.778 ± 1.40 (median: 0)	0.086
• Fatigue	1.818 ± 2.89 (median: 0)	1.222 ± 1.52 (median: 0.5)	0.472
Symptom severity questions related to tsDCS			
• Pain	0.000 ± 0.00 (median: 0)	0.167 ± 0.51 (median: 0)	0.290
• Tingling	0.182 ± 0.40 (median: 0)	0.389 ± 0.78 (median: 0)	0.423
• Itching	0.000 ± 0.00 (median: 0)	0.278 ± 0.83 (median: 0)	0.280
• Burning	0.000 ± 0.00 (median: 0)	0.000 ± 0.00 (median: 0)	
• Electric shock	0.091 ± 0.30 (median: 0)	0.059 ± 0.24 (median: 0)	0.754

[a]Based on 0–10 written analogue scale (0 = No change, 10 = Severe/Significant), values represent the mean and standard deviation.

however, there were no between-group differences in change from D8 to D9 ($P = 0.207$) (Fig. 3C).

Cadence

Both groups demonstrated a significant improvement in cadence on the 10MWT ($P < 0.001$). Participants receiving sham tsDCS demonstrated a greater improvement in cadence at (D2–D8) ($P = 0.046$), although this significance was lost after adjusting for baseline differences in walking speed ($P = 0.091$). Both groups demonstrated retention of cadence gains up to 2 weeks following the period of training, with no between-group differences from D8 to D9 ($P = 0.503$) (Fig. 3c–E).

Stride length

Similar to speed and cadence, both groups demonstrated a significant improvement in stride length on the 10MWT ($P < 0.001$). However, there were no between-group differences in stride length change ($P = 0.3162$). Both groups demonstrated retention of stride length gains up to 2 weeks following the period of training, with no between-group differences from D8 to D9 ($P = 0.711$) (Fig. 3F and G).

Walking capacity

Both groups demonstrated a significant improvement in walking capacity on the 6MWT after BLTT ($P < 0.001$) and reached clinically meaningful importance difference (MCID = 34.4m) [Mean (95% CI): 92 m (62.70–122.9), sham, 41.96 m (25.74, 58.18), anodal] (Tang *et al.*, 2012). Participants receiving sham tsDCS demonstrated a greater improvement in walking capacity, relative to the anodal tsDCS ($P = 0.050$), although this significance was lost after adjusting for baseline differences in walking speed ($P = 0.082$). Both groups demonstrated retention of walking capacity gains up to 2 weeks following the period of training; however, the sham group experienced greater within ($P = 0.005$) and between-group performance ($P = 0.040$) (Fig. 4).

Discussion

Our findings suggest BLTT and tsDCS are safe, feasible and well-tolerated approaches for walking rehabilitation training in stroke. Moreover, preliminary results on walking speed and capacity demonstrated clinically significant and sustained (at least 2 weeks) improvement following six sessions of BLTT.

Backward locomotion treadmill training

Although, BLTT was not tested head-on with overground walking training, it is understood that treadmill allows for more efficient training by enhancing the number of steps achievable over a fixed unit of time, and providing greater aerobic conditioning (Ivey *et al.*, 2008)—a feature which is particularly advantageous in this era of healthcare constraints and decreasing time allotted for physiotherapy by third-party payers. Therefore, it is encouraging that 87% of randomized participants completed the entirety of the BLTT protocol, with 82% completing the training without assistance from a therapist. It is also notable that three out four participants, who initially needed assistance, were able to perform the BLTT task independently by Day 6 of training (Supplementary Table 2).

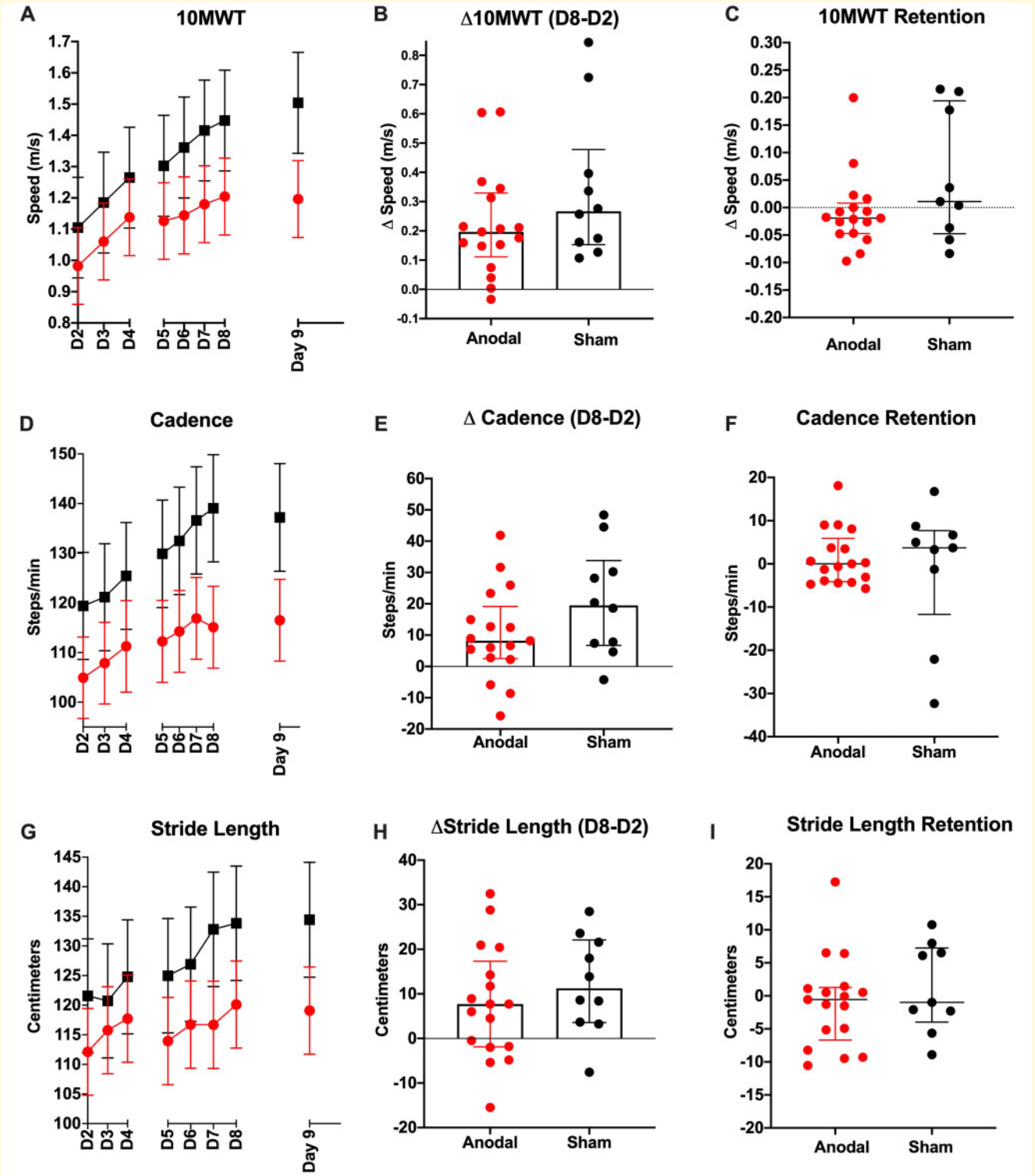


Figure 3 Walking speed and metrics. Mean change in 10MWT speed (**A**), Cadence (**D**) and Stride Length (**G**), during 6 days of BLTT (D2–D7), 24 h, and 2-week follow-up (error bar in SEM). Cumulative training-related changes (D8–D2), for 10MWT (**B**), Cadence (**E**), and Stride Length (**H**), represented as the median and interquartile range. Retention of performance at 2-week follow-up (D9–D8) for 10MWT (**C**), Cadence (**F**), represented as the median and interquartile range (**I**).

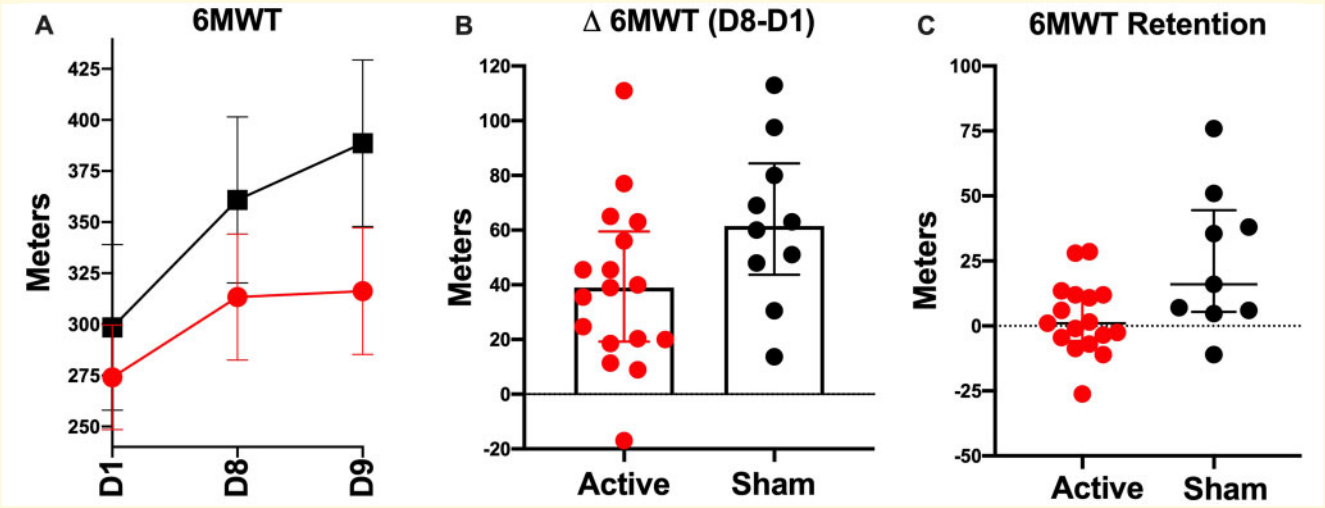


Figure 4 Walking capacity. Mean change in the 6-min walk test (6MWT) at screening baseline (D1), 24-h post-BLTT training, and 2-week follow-up (D9) (**A**), (error bar in SEM). Cumulative training-related change (**B**), and retention of performance at 2-week follow-up (**C**) represented as the median and interquartile range.

Severe walking impairment

Six participants met the classification of severe walking impairment, based on their baseline preferred 10 MW speed (<0.4 m/s). Of these, one participant dropped out entirely from the study on the first day of training, and another stayed in the study but did not meet the criteria for study fidelity. Three others needed assistance with placing the paretic leg backward during training during the early part of the study. In sum, only two of the six participants (33%) were able to independently complete all six BLTT sessions. This finding is akin to previous walking rehabilitation studies that have reported that baseline walking severity level may influence training ability (Burke *et al.*, 2014; Dobkin *et al.*, 2014; Bernhardt *et al.*, 2016; Boyd *et al.*, 2017), which may be associated with the magnitude of post-stroke cognitive and physical limitations in this subgroup, (Kurz *et al.*, 2012; Hawkins *et al.*, 2018; Chatterjee *et al.*, 2019). Therefore, it is possible that our BLTT protocol, in its present form, is too tasking for severely impaired individuals and future protocols will need modification to further accommodate those with severe walking impairment.

Overground walking performance

While BLTT is, in theory, a task-based training approach, its effects extended beyond the improvement in backward walking ability on the treadmill. Our BLTT paradigm was associated with clinically meaningful improvement in overground forward walking speed, step length, cadence and capacity. Participants also noted an improvement in other aspects in quality of life measures such as increased confidence, strength, agility, sleep and mood (Supplementary Fig. 2). Although this study did not directly probe mechanisms for BLTT-related change in walking function, we speculate that factors such as, reduction in spasticity (Thorstensson, 1986; Winter *et al.*, 1989; Schneider and Capaday, 2003; Duysens *et al.*, 2013; El-Basatiny and Abdel-Aziem, 2015), lower extremity and core strengthening (Straube *et al.*, 2014), enhancement of peripheral somatosensory signals to spinal and supraspinal locomotor centres (Takakusaki, 2013; Clark *et al.*, 2014; Afzal *et al.*, 2017; Takakusaki, 2017) and increased exercise capacity (Flynn *et al.*, 1994; Macko *et al.*, 2005; Terblanche *et al.*, 2005) played a role. Future studies are needed to assess these mechanisms, determine the duration of training-related effects and define which physiologic factors and rehabilitation pathways best predict the training outcome.

Transcutaneous spinal direct current stimulation

From a safety standpoint, tsDCS was well tolerated in this study and did not result in any observable adverse effects. This finding is consistent with previous direct current stimulation studies in the literature (Antal *et al.*, 2017).

Although the study was not sufficiently powered to detect significant group differences, our working hypothesis was that BLTT + anodal tsDCS group would perform better than BLTT alone. However, our results showed the contrary, even after adjusting for baseline differences in walking speed. Past studies with direct current stimulation applied over the scalp suggest that anodal stimulation enhances the rate and retention of learned motor task (Nitsche and Paulus, 2000; Reis *et al.*, 2009; Fritsch *et al.*, 2010; Kadosh *et al.*, 2010; Dayan *et al.*, 2013;

Snowball *et al.*, 2013). Likewise, a recent study from our group, albeit in young and neurologically intact individuals, demonstrated that anodal tsDCS over the thoracolumbar vertebra enhanced the acquisition rate and retention of the trained locomotor task (Awosika *et al.*, 2019).

Herein, we propose two potential explanations for this unexpected finding. Firstly, while anodal tsDCS at the spinal segmental level is understood to be facilitatory (Winkler *et al.*, 2010; Lamy *et al.*, 2012; Awosika *et al.*, 2019), its influence on ascending somatosensory pathways has been reported as inhibitory (Cogiamanian *et al.*, 2008; Truini *et al.*, 2011; Lenoir *et al.*, 2018), resulting in a phenomenon known as 'anodal block' (Bhadra and Kilgore, 2004; Cogiamanian *et al.*, 2012). Therefore, one possible explanation for our findings was that anodal tsDCS, in stroke patients, resulted in the inhibition of ascending sensory axons of the somatosensory pathway, which may have diminished the degree of proprioceptive feedback reaching supraspinal locomotor centres during BLTT (Hao and Chen, 2011; Takakusaki, 2013; Clark *et al.*, 2014; El-Basatiny and Abdel-Aziem, 2015; Schweizer *et al.*, 2017; Takakusaki, 2017). While anodal-tsDCS does not appear to hinder performance in younger and neurologically intact individuals, it is widely accepted that stroke survivors rely more heavily on somatosensory processing to maintain functional gait and balance (Clark *et al.*, 2014; Afzal *et al.*, 2017); additionally, somatosensation is known to diminish with age (Callisaya *et al.*, 2008; Chu *et al.*, 2015; Seung-Uk *et al.*, 2016); therefore, we speculate that our study population are more likely more susceptible to perturbations of this pathway.

A second explanation may be the inadequate dosing of anodal tsDCS, which may have led to inhibition, rather than excitation of spinally mediated locomotion. While both groups performed similarly in Week 1 training, the tsDCS group began to experience a decline in the rate of training-related improvement by the second week of training, and at follow-up. Along this line, two groups have reported that direct current stimulation over the scalp may exhibit a time-dependent switch in stimulus effect (Batsikadze *et al.*, 2013; Monte-Silva *et al.*, 2013). While active electrode was placed over the spine, this paradoxical effect with prolonged and frequent stimulation may have altered the spinal locomotor physiology, hindering walking performance. Future electrophysiologic and dosing studies would be useful in testing this working hypothesis, and help to better elucidate the effects of tsDCS at the spinal segmental level.

Limitations

Our study could have been strengthened by the addition of a forward walking training control group, which would have helped to determine the magnitude of BLTT-related improvement in forward walking in comparison to regular overground or forward treadmill training. With this said, the average change in walking speed documented in this study was comparable to previous rigorous rehabilitation studies with much longer training sessions (Duncan *et al.*, 2011; Mehrholz *et al.*, 2017).

Our conclusions regarding training changes in walking speed and capacity between groups must be regarded conservatively, given the between-group differences in baseline performance. Although these differences were not statistically significant, the distribution of severity between groups may have skewed our study results in favour of the control group. Furthermore, since the primary aim of this study was on safety and feasibility and was powered based on our recruitment capabilities, our study was not designed to detect statistically significant differences in walking speed and capacity. Based on the observation that stroke survivors with severe walking impairment had more difficulty completing the BLTT protocol as designed and demonstrated less improvement in overground walking, walking severity will be an *a priori* co-factor in future studies. Moreover, future studies will determine how stroke lesion type, size, location and white matter burden influence training and outcomes.

Conclusion

In summary, this study found that BLTT and tsDCS were both safe and feasible approaches worth further investigation, as possible approaches to optimize walking recovery after stroke. Future, well-powered and dosing-related studies are needed to determine the utility and generalizability of both approaches, alone or combined, in this population.

Supplementary material

Supplementary material is available at *Brain Communications* online.

Competing interests

The authors report no competing interests.

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References

Afzal M, Pyo S, Oh M-K, Park Y, Yoon J. Identifying the effects of using integrated haptic feedback for gait rehabilitation of stroke patients. 2017 International Conference on Rehabilitation Robotics (ICORR) 2017; 2017: 1055–60.

Antal A, Alekseichuk I, Bikson M, Brockmöller J, Brunoni AR, Chen R, et al. Low intensity transcranial electric stimulation: safety, ethical, legal regulatory and application guidelines. Clin Neurophysiol 2017; 128: 1774–809.

Antal A, Polania R, Schmidt-Samoa C, Dechent P, Paulus W. Combining transcranial direct current stimulation with FMRI. Clin Neurophysiol 2010; 41: doi: 10.1055/s-0030-1250980.

Awosika OO, Sandrini M, Volochayev R, Thompson RM, Fishman N, Wu T, et al. Transcutaneous spinal direct current stimulation improves locomotor learning in healthy humans. Brain Stimul 2019; 12: 628–34.

Batsikadze G, Moliadze V, Paulus W, Kuo MF, Nitsche MA. Partially non-linear stimulation intensity-dependent effects of direct current stimulation on motor cortex excitability in humans. J Physiol 2013; 591: 1987–2000.

Bernhardt J, Borschmann K, Boyd L, Carmichael TS, Corbett D, Cramer SC, et al. Moving rehabilitation research forward: developing consensus statements for rehabilitation and recovery research. Int J Stroke 2016; 11: 454–8.

Bhadra N, Kilgore KL. Direct current electrical conduction block of peripheral nerve. IEEE Trans Neural Syst Rehabil Eng 2004; 12: 313–24.

Błażkiewicz M. Muscle force distribution during forward and backward locomotion. Acta Bioeng Biomech 2013; 15: 3–9.

Bocci T, Barloscio D, Vergari M, Rollo A, Rossi S, Priori A, et al. Spinal direct current stimulation modulates short intracortical inhibition. Neuromodulation 2015a; 18: 686–93.

Bocci T, Caleo M, Vannini B, Vergari M, Cogiamanian F, Rossi S, et al. An unexpected target of spinal direct current stimulation: interhemispheric connectivity in humans. J Neurosci Methods 2015b; 254: 18–26.

Bocci T, Marceglia S, Vergari M, Cognetto V, Cogiamanian F, Sartucci F, et al. Transcutaneous spinal direct current stimulation modulates human corticospinal system excitability. J Neurophysiol 2015c; 114: 440–6.

Bocci T, Vannini B, Torzini A, Mazzatenta A, Vergari M, Cogiamanian F, et al. Cathodal transcutaneous spinal direct current stimulation (TsDCS) improves motor unit recruitment in healthy subjects. Neurosci Lett 2014; 578: 75–9.

Boyd LA, Hayward KS, Ward NS, Stinear CM, Rosso C, Fisher RJ, et al. Biomarkers of stroke recovery: consensus-based core recommendations from the stroke recovery and rehabilitation roundtable. Neurorehabil Neural Repair 2017; 31: 864–76.

Boyne P, Dunning K, Carl D, Gerson M, Khoury J, Rockwell B, et al. High-intensity interval training and moderate-intensity continuous training in ambulatory chronic stroke: a feasibility study. Phys Ther 2016; 96: 1533–44.

Burke E, Dobkin BH, Noser EA, Enney LA, Cramer SC. Predictors and biomarkers of treatment gains in a clinical stroke trial targeting the lower extremity. Stroke 2014; 45: 2379–84.

Callisaya ML, Blizzard L, Schmidt MD, Mcginley JL, Lord SR, Srikanth VK. A population-based study of sensorimotor factors affecting gait in older people. Age Ageing 2008; 38: 290–5.

Chatterjee SA, Fox EJ, Daly JJ, Rose DK, Wu SS, Christou EA, et al. Interpreting prefrontal recruitment during walking after stroke: influence of individual differences in mobility and cognitive function. Front Hum Neurosci 2019; 13: 194.

Choi JT, Bastian AJ. Adaptation reveals independent control networks for human walking. Nat Neurosci 2007; 10: 1055–62.

Chu VW, Hornby GT, Schmit BD. Perception of lower extremity loads in stroke survivors. Clin Neurophysiol 2015; 126: 372–81.

Clark DJ, Christou EA, Ring SA, Williamson JB, Doty L. Enhanced somatosensory feedback reduces prefrontal cortical activity during walking in older adults. J Gerontol A Biol Sci Med Sci 2014; 69: 1422–8.

Cogiamanian F, Ardolino G, Vergari M, Ferrucci R, Ciocca M, Scelzo E, et al. Transcutaneous spinal direct current stimulation. Front Psychiatry 2012; 3: 63.

Cogiamanian F, Vergari M, Pulecchi F, Marceglia S, Priori A. Effect of spinal transcutaneous direct current stimulation on somatosensory evoked potentials in humans. Clin Neurophysiol 2008; 119: 2636–40.

Cogiamanian F, Vergari M, Schiaffi E, Marceglia S, Ardolino G, Barbieri S, et al. Transcutaneous spinal cord direct current stimulation inhibits the lower limb nociceptive flexion reflex in human beings. Pain 2011; 152: 370–5.

Dayan E, Censor N, Buch ER, Sandrini M, Cohen LG. Noninvasive brain stimulation: from physiology to network dynamics and back. Nat Neurosci 2013; 16: 838–44.

Dobkin BH. Rehabilitation after stroke. N Engl J Med 2005; 352: 1677–84.

Dobkin BH, Nadeau SE, Behrman AL, Wu SS, Rose DK, Bowden M, et al. Prediction of responders for outcome measures of locomotor experience applied post stroke trial. J Rehabil Res Dev 2014; 51: 39–50.

Duncan PW, Sullivan KJ, Behrman AL, Azen SP, Wu SS, Nadeau SE, et al. Body-weight–supported treadmill rehabilitation after stroke. N Engl J Med 2011; 364: 2026–36.

Duysens J, Groote F, Jonkers I. The flexion synergy, mother of all synergies and father of new models of gait. Front Comput Neurosci 2013; 7: 14.

El-Basatiny HM, Abdel-Aziem A. Effect of backward walking training on postural balance in children with hemiparetic cerebral palsy: a randomized controlled study. Clin Rehabil 2015; 29: 457–67.

Fiocchi S, Ravazzani P, Priori A, Parazzini M. Cerebellar and spinal direct current stimulation in children: computational modeling of the induced electric field. Front Hum Neurosci 2016; 10: 522.

Flynn TW, Connery SM, Smutok MA, Zeballos RJ, Weisman IM. Comparison of cardiopulmonary responses to forward and backward walking and running. Med Sci Sports Exerc 1994; 26: 89–94.

Foster H, Demark L, Spigel PM, Rose DK, Fox EJ. The effects of backward walking training on balance and mobility in an individual with chronic incomplete spinal cord injury: a case report. Physiother Theory Pract 2016; 32: 536–45.

Fregni F, Grecco L, Li S, Michel S, Castillo-Saavedra L, Mourdoukoutas A, et al. Transcutaneous spinal stimulation as a therapeutic strategy for spinal cord injury: state of the art. J Neurorestoratol 2015; 3: 73–82.

Fritsch B, Reis J, Martinowich K, Schambra HM, Ji Y, Cohen LG, et al. Direct current stimulation promotes BDNF-dependent synaptic plasticity: potential implications for motor learning. Neuron 2010; 66: 198–204.

Fritz NE, Worstell AM, Kloos AD, Siles AB, White SE, Kegelmeyer DA. Backward walking measures are sensitive to age-related changes in mobility and balance. Gait Posture 2013; 37: 593–7.

Fulk GD, He Y, Boyne P, Dunning K. Predicting home and community walking activity poststroke. Stroke 2017; 48: 406–11.

Geiger M, Supiot A, Zory R, Aegerter P, Pradon D, Roche N. The Effect of transcranial direct current stimulation (tDCS) on locomotion and balance in patients with chronic stroke: study protocol for a randomised controlled trial. Trials 2017; 18: 492.

Geroin C, Picelli A, Munari D, Waldner A, Tomelleri C, Smania N. Combined transcranial direct current stimulation and robot-assisted gait training in patients with chronic stroke: a preliminary comparison. Clin Rehabil 2011; 25: 537–48.

Grasso R, Bianchi L, Lacquaniti F. Motor patterns for human gait: backward versus forward locomotion. J Neurophysiol 1998; 80: 1868–85.

Hao W-Y, Chen Y. Backward walking training improves balance in school-aged boys. Sports Med Arthrosc Rehabil Ther Techno 2011; 3: 1–7.

Harvey RL, Edwards D, Dunning K, Fregni F, Stein J, Laine J, et al.; on behalf of the NICHE Trial Investigators. Randomized sham-controlled trial of navigated repetitive transcranial magnetic stimulation for motor recovery in stroke. Stroke 2018; 49: 2138–46.

Hawkins KA, Fox EJ, Daly JJ, Rose DK, Christou EA, Mcguirk TE, et al. Prefrontal over-activation during walking in people with mobility deficits: interpretation and functional implications. Hum Mov Sci 2018; 59: 46–55.

Hoogkamer W, Meyns P, Duysens J. Steps forward in understanding backward gait: from basic circuits to rehabilitation. Exerc Sport Sci Rev 2014; 42: 23–9.

Hubli M, Dietz V, Schrafl-Altermatt M, Bolliger M. Modulation of spinal neuronal excitability by spinal direct currents and locomotion after spinal cord injury. Clin Neurophysiol 2013; 124: 1187–95.

Ivey FM, Hafer-Macko CE, Macko RF. Task-oriented treadmill exercise training in chronic hemiparetic stroke. J Rehabil Res Dev 2008; 45: 249–60.

Jansen K, Groote F, Massaad F, Meyns P, Duysens J, Jonkers I. Similar muscles contribute to horizontal and vertical acceleration of center of mass in forward and backward walking: implications for neural control. J Neurophysiol 2012; 107: 3385–96.

Jeffery DT, Norton JA, Roy FD, Gorassini MA. Effects of transcranial direct current stimulation on the excitability of the leg motor cortex. Exp Brain Res 2007; 182: 281–7.

Jones PS, Pomeroy VM, Wang J, Schlaug G, Marrapu TS, Geva S, et al.; for the SWIFT-Cast Investigators. Does stroke location predict walk speed response to gait rehabilitation? Hum Brain Mapp 2016; 37: 689–703.

Kadosh R, Soskic S, Iuculano T, Kanai R, Walsh V. Modulating neuronal activity produces specific and long-lasting changes in numerical competence. Curr Biol 2010; 20: 2016–20.

Kang N, Summers JJ, Cauraugh JH. Transcranial direct current stimulation facilitates motor learning post-stroke: a systematic review and meta-analysis. J Neurol Neurosurg Psychiatry 2016; 87: 345–55.

Kluding PM, Dunning K, O'Dell MW, Wu SS, Ginosian J, Feld J, et al. Foot drop stimulation versus ankle foot orthosis after stroke. Stroke 2013; 44: 1660–9.

Kuck A, Stegeman DF, Van Asseldonk E. Modeling trans-spinal direct current stimulation for the modulation of the lumbar spinal motor pathways. J Neural Eng 2017; 14: 056014.

Kurz MJ, Wilson TW, Arpin DJ. Stride-time variability and sensorimotor cortical activation during walking. Neuroimage 2012; 59: 1602–7.

Lamy CJ, Ho C, Badel A, Arrigo RT, Boakye M. Modulation of soleus H reflex by spinal DC stimulation in humans. J Neurophysiol 2012; 108: 906–14.

Langhorne P, Bernhardt J, Kwakkel G. Stroke rehabilitation. Lancet 2011; 377: 1693–702.

Lenoir C, Jankovski A, Mouraux A. Anodal transcutaneous spinal direct current stimulation (tsDCS) selectively inhibits the synaptic efficacy of nociceptive transmission at spinal cord level. Neuroscience 2018; 393: 150–63. (Physiol Rep 4 2016):

Lord SE, Mcpherson K, Mcnaughton HK, Rochester L, Weatherall M. Community ambulation after stroke: how important and obtainable is it and what measures appear predictive? Arch Phys Med Rehabil 2004; 85: 234–9.

Macko RF, Ivey FM, Forrester LW. Task-oriented aerobic exercise in chronic hemiparetic stroke: training protocols and treatment effects. Top Stroke Rehabil 2005; 12: 45–57.

Macko RF, Ivey FM, Forrester LW, Hanley D, Sorkin JD, Katzel LI, et al. Treadmill exercise rehabilitation improves ambulatory function and cardiovascular fitness in patients with chronic stroke a randomized, controlled trial. Stroke 2005; 36: 2206–11.

Madhavan S, Stinear JW. Focal and bidirectional modulation of lower limb motor cortex using anodal transcranial direct current stimulation. Brain Stimul 2010; 3: 42–50.

Marangolo P, Fiori V, Shofany J, Gili T, Caltagirone C, Cucuzza G, et al. Moving beyond the brain: transcutaneous spinal direct current stimulation in post-stroke aphasia. Front Neurol 2017; 8: 400.

Mehrholz J, Thomas S, Elsner B. Treadmill training and body weight support for walking after stroke. Cochrane Database Syst Rev 2017; 23: CD002840.

Michaelsen SM, Ovando ACC, Romaguera F, Ada L. Effect of backward walking treadmill training on walking capacity after stroke: a randomized clinical trial. Int J Stroke 2014; 9: 529–32.

Monte-Silva K, Kuo M-F, Hessenthaler S, Fresnoza S, Liebetanz D, Paulus W, et al. Induction of late LTP-like plasticity in the human motor cortex by repeated non-invasive brain stimulation. Brain Stimul 2013; 6: 424–32.

Musienko PE, Zelenin PV, Lyalka VF, Gerasimenko YP, Orlovsky GN, Deliagina TG. Spinal and supraspinal control of the direction of stepping during locomotion. J Neurosci 2012; 32: 17442–53.

Nilsson L, Carlsson J, Danielsson A, Fugl-Meyer A, Hellström K, Kristensen L, et al. Walking training of patients with hemiparesis at an early stage after stroke: a comparison of walking training on a treadmill with body weight support and walking training on the ground. Clin Rehabil 2001; 15: 515–27.

Nitsche MA, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. J Physiol 2000; 527: 633–9.

Ordway JD, Laubach LL, Vanderburgh PM, Jackson KJ. The effects of backwards running training on forward running economy in trained males. J Strength Cond Res 2016; 30: 763–7.

Parazzini M, Fiocchi S, Liorni I, Rossi E, Cogiamanian F, Vergari M, et al. Modeling the current density generated by transcutaneous spinal direct current stimulation (tsDCS). Clin Neurophysiol 2014; 125: 2260–70.

Perry J, Garrett M, Gronley JK, Mulroy SJ. Classification of walking handicap in the stroke population. Stroke 1995; 26: 982–9.

Priori A, Ciocca M, Parazzini M, Vergari M, Ferrucci R. Transcranial cerebellar direct current stimulation and transcutaneous spinal cord direct current stimulation as innovative tools for neuroscientists. J Physiol 2014; 592: 3345–69.

Pritchett K, Pritchett R. Chocolate milk: a post-exercise recovery beverage for endurance sports. Med Sport Sci 2012; 59: 127–34.

Reis J, Schambra HM, Cohen LG, Buch ER, Fritsch B, Zarahn E, et al. Noninvasive cortical stimulation enhances motor skill acquisition over multiple days through an effect on consolidation. Proc Natl Acad Sci USA 2009; 106: 1590–5.

Rose DK, Demark L, Fox EJ, Clark DJ, Wludyka P. A backward walking training program to improve balance and mobility in acute stroke. J Neurol Phys Ther 2018; 42: 12–21.

Schlaug G, Cohen LG. Brain repair after stroke. Cambridge University Press; 2010. p. 207–18.

Schmid A, Duncan PW, Studenski S, Lai S, Richards L, Perera S, et al. Improvements in speed-based gait classifications are meaningful. Stroke 2007; 38: 2096–100.

Schneider C, Capaday C. Progressive adaptation of the soleus h-reflex with daily training at walking backward. J Neurophysiol 2003; 89: 648–56.

Schweizer L, Meyer-Frießem CH, Zahn PK, Tegenthoff M, Schmidt-Wilcke T. Transcutaneous spinal direct current stimulation alters resting-state functional connectivity. Brain Connect 2017; 7: 357–65.

Seung-Uk KO, Simonsick EM, Deshpande N, Studenski S, Ferrucci L. Ankle proprioception-associated gait patterns in older adults. Med Sci Sports Exerc 2016; 48: 2190–4.

Snowball A, Tachtsidis I, Popescu T, Thompson J, Delazer M, Zamarian L, et al. Long-term enhancement of brain function and cognition using cognitive training and brain stimulation. Curr Biol 2013; 23: 987–92.

Stacy LF, Ashlee LP, Anna CR, Skylar CO, Erin DR. An intense intervention for improving gait, balance, and mobility for individuals with chronic stroke: a pilot study. J Neurol Phys Ther 2007; 31: 71–6.

Stagg CJ, Kischka U, Matthews PM, Johansen-Berg H. Transcranial direct current stimulation (tDCS)-induced changes in motor function in chronic stroke patients are associated with renormalisation of motor-related cortical activity. Neuroimage 2009; 47: S116.

Straube DD, Holleran CL, Kinnaird CR, Leddy AL, Hennessy PW, Hornby GT. Effects of dynamic stepping training on nonlocomotor tasks in individuals poststroke. Phys Ther 2014; 94: 921–33.

Studenski S, Perera S, Wallace D, Chandler JM, Duncan PW, Rooney E, et al. Physical performance measures in the clinical setting. J Am Geriatr Soc 2003; 51: 314–22.

Takakusaki K. Neurophysiology of gait: from the spinal cord to the frontal lobe. Mov Disord 2013; 28: 1483–91.

Takakusaki K. Functional neuroanatomy for posture and gait control. J Mov Disord 2017; 10: 1–17.

Tang A, Eng JJ, Rand D. Relationship between perceived and measured changes in walking after stroke. J Neurol Phys Ther 2012; 36: 115–21.

Terblanche E, Page C, Kroff J, Venter RE. The effect of backward locomotion training on the body composition and cardiorespiratory fitness of young women. Int J Sports Med 2005; 26: 214–9.

Thorstensson A. How is the normal locomotor program modified to produce backward walking? Exp Brain Res 1986; 61: 664–8.

Truini A, Vergari M, Biasiotta A, Cesa LS, Gabriele M, Stefano DG, et al. Transcutaneous spinal direct current stimulation inhibits nociceptive spinal pathway conduction and increases pain tolerance in humans. Eur J Pain 2011; 15: 1023–7.

Vergari M, Cogiamanian F, Pulecchi F, Marceglia S, Tadini L, Ferrucci R, et al. Non-invasive modulation of spinal cord function with transcutaneous direct current (DC) stimulation. Brain Stimul 2008; 1: 304.

Weiguo S, Dennis QT, Marom B, John HM. Transspinal direct current stimulation immediately modifies motor cortex sensorimotor maps. J Neurophysiol 2015; 113: 2801–11.

Wernig A, Wernig S. The trouble with "body weight support" in treadmill training. Arch Phys Med Rehabil 2010; 91: 1478.

Winkler T, Hering P, Straube A. Spinal DC stimulation in humans modulates post-activation depression of the H-reflex depending on current polarity. Clin Neurophysiol 2010; 121: 957–61.

Winter DA, Pluck N, Yang JF. Backward walking: a simple reversal of forward walking? J Motor Behav 1989; 21: 291–305.

Yang Y-R, Yen J-G, Wang R-Y, Yen L-LL, Lieu F-K. Gait outcomes after additional backward walking training in patients with stroke: a randomized controlled trial. Clin Rehabil 2005; 19: 264–73.

Yeon-Gyu J, Jung-Wan K. The effects of treadmill walking combined with obstacle-crossing on walking ability in ambulatory patients after stroke: a pilot randomized controlled trial. Top Stroke Rehabil 2016; 23: 406–12.

Zachary T, Laura B, Courtney K, Gabriela P, Lorraine S, Jeffrey H. The efficacy of treadmill training on balance dysfunction in individuals with chronic stroke: a systematic review. Top Stroke Rehabil 2017; 24: 1–8.

Zaghloul A. Trans-spinal direct current stimulation modifies spinal cord excitability through synaptic and axonal mechanisms. Physiol Rep 2014; 2: 1–17.

Zaghloul A. Modulation of gamma and alpha spinal motor neurons activity by trans-spinal direct current stimulation: effects on reflexive actions and locomotor activity. Physiol Rep 2016; 4: 1–22.