HHS Public Access

Author manuscript

Spinal Cord. Author manuscript; available in PMC 2022 November 07.

Published in final edited form as:

Spinal Cord. 2022 November ; 60(11): 971–977. doi:10.1038/s41393-022-00801-1.

Feasibility of transcutaneous spinal direct current stimulation combined with locomotor training after spinal cord injury

Kelly A. Hawkins[1], **Louis A. DeMark**[2], **Arian Vistamehr**[2], **Hannah J. Snyder**[2], **Christy Conroy**[2], **Clayton Wauneka**[2], **Geneva Tonuzi**[2], **David D. Fuller**[1], **David J. Clark**[3,4], **Emily J. Fox**[1,2]

[1]Department of Physical Therapy, University of Florida, Gainesville, FL, USA

[2]Brooks Rehabilitation, Jacksonville, FL, USA

[3]Brain Rehabilitation Research Center of Excellence, North Florida/South Georgia Veterans Health System, Gainesville, FL, USA

[4]Department of Aging and Geriatric Research, University of Florida, Gainesville, FL, USA

Abstract

Study Design: Feasibility study, consisting of random-order, cross-over study of a single intervention session, followed by a parallel-arm study of 16 sessions

Objectives: To investigate the feasibility of a novel combinatorial approach with simultaneous delivery of transcutaneous spinal direct current stimulation (tsDCS) and locomotor training (tsDCS+LT) after spinal cord injury, compared to sham stimulation and locomotor training (sham+LT), and examine preliminary effects on walking function.

Setting: Clinical research center in the southeastern United States

Methods: Eight individuals with chronic incomplete spinal cord injury (ISCI) completed the two-part protocol. Feasibility was assessed based on safety (adverse responses), tolerability (pain, spasticity, skin integrity), and protocol achievement (session duration, intensity). Walking function was assessed with the 10-meter and 6-minute walk tests.

Results: There were no major adverse responses. Minimal reports of skin irritation and musculoskeletal pain were consistent between groups. Average training peak heart rate as percent of maximum (mean(SD); tsDCS+LT: 66(4)%, sham+LT: 69(10)%) and Borg ratings of perceived exertion (tsDCS+LT: 17.5(1.2), sham+LT: 14.4(1.8)) indicate both groups trained at high

Corresponding author: Emily Fox (ejfox@phhp.ufl.edu).

Author Contribution Statement: DDF, DJC, and EJF conceived and designed the study. KAH, LAD, AV, HJS, CC, CW, GT and EJF collected the data. KAH, LAD, HJS and EJF performed the analysis and interpretation. KAH and EJF drafted the article. KAH, LAD, AV, HJS, CC, CW, GT, DDF, DJC, and EJF critically reviewed the draft and provided revisions. KAH, LAD, AV, HJS, CC, CW, GT, DDF, DJC, and EJF approved the final version to be published.

Competing interests: The authors declare no competing interests.

Ethic Approval: The Institutional Review Board at the University of Florida approved the study (201801582) and all research was performed in accordance with the Declaration of Helsinki. We certify that all applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during the course of this research.

intensities. Walking speed gains exceeded the minimal clinically important difference (MCID) in three of four who received tsDCS+LT (0.18(0.29) m/s) and one of four in sham+LT (−0.05(0.23) m/s). Gains in walking endurance exceeded the MCID in one of four in each group (tsDCS+LT: 36.4(69.0) m, sham+LT: 4.9(56.9) m).

Conclusions: Combinatorial tsDCS and locomotor training is safe and feasible for individuals with chronic ISCI, even those with considerable walking impairment. Study outcomes support the need to investigate the efficacy of this approach.

Introduction

After incomplete spinal cord injury (SCI), rehabilitation can promote walking recovery by capitalizing on intact spinal circuits [1]. Through repetitive walking practice, signals from residual descending pathways and afferent inputs promote activation of lumbar spinal circuits critical for stepping, limb coordination and reflex modulation across the step cycle [2–5]. However, spinal excitability remains reduced post-SCI and the circuits reorganize as a result of altered inputs [6–8]. Consequently, walking rehabilitation is often only partially effective and walking deficits persist.

To amplify the benefits of rehabilitation, neurorehabilitation leaders have encouraged combining complimentary interventions, such as electrical stimulation and task-specific training [9–11]. In walking rehabilitation, the addition of transcutaneous spinal direct current stimulation (tsDCS) may be an appropriate combinatorial approach. tsDCS is a mild, non-invasive form of electrical stimulation targeting modulation of spinal reflexes, corticospinal excitability, and spinal processing of sensory inputs [12–16]. Importantly, tsDCS increases the amplitude of spinal reflexes associated with locomotor behaviors in individuals post-SCI [17]. tsDCS may enhance the therapeutic effect of walking rehabilitation if applied in combination, particularly if the intervention also targets residual spinal circuits. Locomotor training (LT), an established rehabilitation strategy, is well suited as it aims to facilitate spinal locomotor output by promoting task-specific input to lumbar circuits below the injury level [18]. The combined approach might provide more potent activation of the spinal neural circuits, driving greater neuroplastic recovery of function. tsDCS alters neuron membrane potentials but does not, by itself, elicit neuron action potentials. Rather, when spinal circuits are excited simultaneously by motor behaviors and tsDCS, those circuits may be strengthened to a greater extent through Hebbian neuroplasticity (“neurons that fire together wire together”) [19].

Currently, it is not known if a rehabilitation strategy involving repeated application of tsDCS in combination with LT is safe and feasible for individuals after SCI. Most prior research on tsDCS was performed in a single session while participants were recumbent or resting [13–16]. The neuromodulatory effects of tsDCS applied during LT could result in unfavorable changes in pain, spasticity or motor output in people with SCI. Furthermore, commercially available direct current stimulation electrodes use non-adhesive, saline-soaked sponges that could cause skin irritation under the tightly fitting harness used to provide body weight support during training, particularly since SCI alters the integumentary systems and impairs

sensation [20, 21]. In addition, there are potential instrumentation challenges when used during walking, such as preventing electrodes from shifting during vigorous movement.

The limited evidence of tsDCS applied during walking rehabilitation and potential adverse effects indicates that feasibility should be established prior to next steps in clinical trials and potential clinical translation. Feasibilities studies can be defined as “research done before a main study in order to answer the question ‘Can this study be done?’…and to estimate important parameters that are needed to design the main study”[22]. Recently, two small feasibility studies combined a walking intervention with a different form of electrical stimulation (50 Hz, biphasic pulses) in individual post-SCI [23, 24]. Similar to the effects of tsDCS, noninvasive alternating current spinal stimulation has the potential to increase voluntary motor responses, particularly when combined with activity-based rehabilitation [25]. Findings suggested a positive influence on walking recovery and spasticity. However, the high current applied in one study (39 to 100 mA) resulted in an average pain rating between three and four out of 10 during the intervention [23]. Furthermore, the stimulation induced back and abdominal muscle contractions and participants reported feeling “intense tightness” around the electrode sites. The use of a high-frequency carrier wave has been introduced to reduce discomfort during transcutaneous alternating current electrical stimulation protocols, however, the carrier frequency has no effect on tolerance when compared in relation to the motor threshold [26]. Application at the lumbar level continued to cause reports of tightness of the trunk muscles when parameters were optimized for facilitating muscle activity to maintain a static standing position [27]. Tolerance of alternating current with a carrier frequency has not been reported during walking activities in those with incomplete injuries. In contrast, tsDCS uses a very low current (2.5 mA), sub-motor activation threshold, and is either barely perceived as a tingling or not felt at all. Furthermore, combined tsDCS and LT is feasible and safe for individuals post-stroke [28] suggesting investigation in individuals post-SCI is warranted; the neuromodulatory effects of tsDCS may augment LT outcomes with less side effects than other forms of spinal electrical stimulation.

To provide critical preparatory data for clinical studies on the efficacy of combining tsDCS and LT, this feasibility study examined the question “can the study be done?” in individuals with incomplete SCI, examining a single session and a 16-session training protocol. The central hypothesis guiding this study was simultaneous delivery of tsDCS and LT is a feasible and tolerable intervention for individuals with incomplete SCI. Our secondary hypothesis was combined tsDCS with LT would show preliminary evidence of greater improvements in walking speed and endurance compared to sham tsDCS and LT.

Methods

Participants

Individuals with chronic motor incomplete SCI were recruited through an Institutional Review Board-approved research recruitment registry, the clinicaltrials.gov Web site (NCT03702842), flyers, local health care providers and researchers. The Institutional Review Board at the University of Florida approved the study and all participants provided informed consent. Study inclusion criteria included an incomplete SCI more than one year

before enrollment, the ability to walk a short distance, and no other medical conditions or physical limitations preventing safe participation. All inclusion and exclusion criteria are listed in the Table 1. Participants were screened prior to initiating the study procedures to ensure eligibility. Screening included an in-person participant interview and physical examination as well as review of medical records.

Study Design

The study had two parts. First, a two-way cross-over design was used to test the feasibility of the combined intervention within a single session (Figure 1). Since injury characteristics are heterogeneous and LT parameters often vary to accommodate individual ability, the single-session design allowed a controlled, within-subject comparison of the two stimulation protocols; all eight participants completed two sessions in which they received either active tsDCS and LT (tsDCS+LT) or a sham tsDCS protocol and LT (sham+LT). By having each participant complete matched sessions (i.e., walking parameters and treadmill variables were consistent across the two sessions), each subject's response to active versus sham stimulation could be compared. The sessions were conducted on separate days at least 48 hours apart to minimize carryover effects and the order was counter-balanced across participants.

Secondly, the feasibility of undergoing repeated exposure to the combinatorial intervention was assessed to further explore a scenario resembling clinical application. Assessment before and after the training protocols also provided data for the secondary purpose of exploring effects on walking function. A parallel group design was used wherein the participant received either tsDCS+LT or sham+LT throughout a 16-session training (four times per week for four weeks). Randomization after enrollment was completed with web-based random number generation and concealed from participants, intervention therapists and assessors.

Intervention Procedures

tsDCS and sham tsDCS—During tsDCS+LT sessions, 30 minutes of tsDCS was delivered continuously at 2.5 mA (Soterix Medical, Inc., New York, NY) during LT. After cleaning the skin with an alcohol wipe, a single anodal electrode (4.5 × 4.5 cm carbon rubber electrode embedded within a thin 5 × 10 cm sponge; EasyPad, Soterix Medical Systems, New York, NY) was placed posteriorly, centered over the spinous processes of the eleventh and twelfth thoracic vertebrae. Two cathodal electrodes (4.5 × 4.5 cm carbon rubber electrodes, 5 × 7 cm sponges) were placed on the abdomen, about 2 centimeters lateral to the umbilicus on each side and level with the posterior electrode. This electrode placement was used to target the locomotor circuits in the lumbar spinal cord [29]. The position of the electrodes was maintained with an elastic wrap. Sham+LT sessions involved an identical setup, but the tsDCS ramped up to 2.5 mA then back down after 30 seconds and remained off. This standard sham protocol provides the sensation of active tsDCS because participants habituate to the cutaneous sensation of active tsDCS within about a minute.

Locomotor training—LT was conducted in accordance with established procedures; task-specific training was performed at high intensities while promoting the appropriate afferent

feedback from stepping and minimizing compensations [1, 30, 31]. During treadmill LT, the lead physical therapist, a clinician with LT and SCI expertise, facilitated intense stepping practice by adjusting parameters such as body weight support, therapist assistance and bout durations based on the participant's ability. Similarly, during overground LT, intensity was encouraged by minimizing reliance on assistive devices and providing therapist assistance and passive harness support only when needed for safety. To ensure adequate training intensity, heart rate was continuously monitored using an optical sensor (Polar; Bethpage, NY) with the goal of maintaining heart rate at 70 to 80 percent of age-predicted maximum, and rate of perceived exertion (RPE) was targeted to reach between 14 and 17 ("hard" to "very hard") on the Borg scale (6–20 rating scale). During each walking bout, training parameters were recorded, and training parameters were adjusted to maintain intensity within the target range. As walking performance improved, training intensity was adjusted for each individual by increasing walking speed and bout duration, or reducing rest duration, therapist assistance, and body weight support.

The training intensity goals were the same for the single-session and 16-session protocols. However, during the single sessions training parameters were tightly controlled; LT only occurred on a treadmill and during the 30 minutes of tsDCS. Therefore, the timing of the intervention, time intervals before and after testing, and procedures were consistent across all participants. Since participants' walking abilities varied, sessions were closely monitored so that training parameters (i.e., walking speed, percent of body weight support, walking bout and rest break lengths, and assistance levels) were consistent within the two single-session visits for each participant. During the 16-session training, all participants were encouraged to achieve a total stepping time of 30 minutes on the treadmill and 10 minutes overground, taking rest breaks as needed [7, 32]. Therefore, depending on the duration of rest bouts, the session extended beyond the duration of the tsDCS.

Assessment of feasibility

Protocol achievement—Protocol achievement during the single-session visits was based on whether tsDCS and LT parameters (e.g., duration of tsDCS application, LT walking and rest bout durations, treadmill speeds, body weight support, and trainer assistance) were consistent between sessions. For the training portion of the study, protocol achievement was primarily assessed through the participants' ability to complete the prescribed 16-session intervention. Therefore, we tracked the parameters assessed during the single sessions and added others, such as training intensity.

Tolerance—During all sessions, tolerance was assessed by monitoring for adverse changes in pain, spasticity, and motor function as well as skin irritation or discomfort at the electrode sites. During the 16-session training portion, participants were asked at each session to respond to the prompt "since the last session, have you experienced any changes in pain, spasticity, sleep patterns or medication use?".

Safety—Safety was assessed by monitoring blood pressure and heart rate. An automatic blood pressure gauge was used to assess blood pressure at least three times during each session: prior to treadmill LT, after treadmill LT/before overground LT, and immediately

after overground LT. If the participant reported symptoms of orthostatic hypotension or autonomic dysregulation, blood pressure was also assessed during rest breaks in the training to assure safety. Heart rate was measured continuously with an optical heart rate monitor over the brachial artery, allowing close monitoring of safety and training intensity throughout training. Since autonomic dysreflexia is a common serious condition after SCI, changes in blood pressure and subjective reports were carefully considered. Physical therapists experienced in walking rehabilitation post-SCI also monitored for any other adverse physiological responses or other serious issue that would constitute a health risk (e.g., wound development, severe pain, new onset of neuropathic pain).

Assessment of Walking Performance

Walking performance was assessed before and after the 16-session protocol. The 10-meter walk test was used to assess walking speed [33]. Participants walked overground at their fastest comfortable speed using their typical assistive device with the minimally necessary assistance and bracing to maintain safety. Walking endurance was assessed using the 6-minute walk test [33].

Analysis

Descriptive statistics are provided as group mean (standard deviation) for demographic information as well as training parameters and outcomes in each group. Due to the small group size (n=4) and likelihood that statistical analysis would yield inaccurate results, effect sizes and non-parametric tests are not reported [34].

Results

Participants

Eight individuals were screened. Initially, three did not pass the screening (current infection, participation in other walking study, injury acuity) and were later rescreened and passed. Consequently, a total of 11 screenings were completed to enroll eight participants. All completed the study (n=4 in each training intervention group). Demographic information is included in Table 2.

Feasibility

Protocol Achievement—All participants completed both single sessions and 16 sessions of training as prescribed. During the single sessions, each participant was able to replicate their LT parameters (e.g., walking bout length, speed) between the tsDCS+LT and sham+LT sessions, allowing for comparison of the sessions. Participants completed five to seven walking bouts ranging from one to four minutes within the 30 minutes of tsDCS. Total stepping time varied from 9.6 to 20 minutes and walking speed ranged from 0.2–0.7 meters per second. During the 16-session training, the groups had similar average treadmill stepping times (tsDCS+LT: 28.6(1.5) min, sham+LT: 28.7(1.6) min) and overground stepping times (tsDCS+LT: 7.3(2.4) min, sham+LT: 8.7(1.6) min). Subjective reports of fatigue or musculoskeletal pain were always the reason for not completing the entire protocol. During treadmill LT, body weight support averaged 32% for participants in the tsDCS+LT group and 24% in the sham+LT group. Across both groups, all but one participant (participant

01) required physical assistance to maintain upright posture and rhythmic stepping during treadmill LT. Five participants required assistance at the trunk and bilateral lower extremities for all treadmill LT sessions. During overground LT, seven of the eight participants used an assistive device or handhold assistance; five participants required use of a rolling walker or bilateral handhold assistance. Overall, examination of training intensity outcomes (i.e., peak heart rate response during training, treadmill training RPE, overground training RPE, steps per session, training treadmill speed and increase in training treadmill speed compared to their pre-training speed) indicated that the groups reached similar levels of intensity. Intensity parameters are detailed in Table 3.

Tolerability—No discomfort or other side effects were reported during the single session of tsDCS+LT and, overall, the participants receiving tsDCS+LT during training tolerated the repeated exposure. Two minor issues related to the skin under the electrodes were noted. One participant in the tsDCS+LT group, 01, reported itchiness in the area of the posterior electrode; examination revealed dry skin, likely the result of the repeated skin preparation with alcohol, and the issue resolved with the use of lotion in the evenings. Another participant in the tsDCS+LT group, 02, developed an abrasion near the edge of the posterior electrode that was covered for future sessions. When a similar abrasion developed in a member of the sham+LT group, 06, it was determined that an exposed rough edge on the strap's Velcro for attaching the electrodes was the cause. While multiple factors (electrode moisture, post-SCI skin changes, older age) may have contributed to skin integrity issues, covering the rough edge for the subsequent participants resolved the issue.

There was only one participant receiving tsDCS who reported a direct side effect from the stimulation; participant 11 (randomized to sham+LT) reported a burning sensation during the 30 seconds of stimulation in her third intervention session and the intensity was lowered to 1 mA for the 30 seconds. In subsequent sessions, she also reported a mild burning sensation but tolerated the normal intensity. No other participants reported pain caused by the stimulation.

A few other side effects were noted during training. Two participants in the sham+LT group, 08 and 11, had musculoskeletal pain that delayed intervention for at least one session. One participant in the tsDCS+LT group, 02, reported a nighttime episode of brief, intense foot pain. This individual also reported periods of increased spasticity or spasms that mildly affected his sleep. Similarly, one individual in the sham+LT group, 08, also reported similar fluctuations in spasticity. The influence of tsDCS cannot be definitively ruled out, but participants in the tDCS+LT group did not appear to have worse side effects than those in the sham+LT group. It is more likely the intense training parameters, a marked increase in physical activity, and high repetitions of stepping contributed to these reports.

Safety—In seven out of eight participants, there were no adverse events. During both the tsDCS+LT and sham+LT single sessions, one participant, 08, experienced a decrease in heart rate and increase in blood pressure while stepping, consistent with onset of autonomic dysregulation. Each episode resolved with a seated rest break. Participant 08, who was randomized to the sham+LT group, continued to have similar episodes during his first seven

training sessions, but the issue subsided gradually and resolved for later training sessions. No other adverse responses were noted during the training portion of the study.

16-Session Training Walking Performance Outcomes

Assessment of walking speed with the 10-meter walk test following the 16-session training protocol revealed an average walking speed change of 0.18(0.29) m/s in the tsDCS+LT group compared to an average change of −0.05(0.23) m/s in the sham+LT group. Three participants in the tsDCS+LT group exceeded the test's minimal clinically important difference (MCID; 0.06 m/s) compared to only one participant in the sham+LT group [35]. Assessment of walking endurance with the 6-minute walk test demonstrated an average improvement of 36.4(69.0) m in the tsDCS+LT group and 4.9(56.9) m in the sham+LT group. One participant in each group reached the MCID (0.10 m/s or 36 m)[36]. Individual results are included in Table 4.

Discussion

The feasibility outcomes (protocol achievement, tolerance and safety) in a small, diverse sample indicate combined tsDCS and LT is safe and feasible for individuals with motor incomplete SCI. The participants had varied injury characteristics and walking abilities indicating that those with both low and high walking function can participate in this clinically-translatable combinatorial intervention. Furthermore, all individuals were able to complete the protocol/training at high intensities based on heart rate and perceived exertion. Gains in walking function after 16 sessions indicate the potential of this intervention to improve walking function. Overall, study outcomes are encouraging in this small cohort of individuals indicating further investigation of efficacy is warranted.

Feasibility

Feasibility was demonstrated by this study in a small group with individuals who had a range of injury characteristics consistent with those who participated in prior studies of SCI walking rehabilitation [7]. Furthermore, the majority of the group had severe walking impairment and were wheelchair dependent, suggesting that this intervention is feasible for most individuals who pursue walking rehabilitation interventions. The addition of the tsDCS protocol did not create a barrier to achieving two critical ingredients in walking rehabilitation after SCI: the amount and intensity of stepping practice [30, 37]. Training frequency and stepping time were consistent with prior studies that reported these variables [30, 32, 38]. It was also feasible to deliver the intervention in a manner consistent with recent reports of high-intensity training [30].

An important indicator of feasibility is the absence of side effects and adverse events. Individuals post-SCI have several health concerns to consider, particularly with respect to intense walking interventions and electrical stimulation. First, nearly 60% of individuals with SCI have impaired autonomic regulation, altering the precise control of heart rate and blood pressure adjustments that typically accompany postural changes and exertion during training. Moreover, serious complications such as autonomic dysreflexia can be triggered by a variety of stimuli causing unsafe elevations in blood pressure and limiting the ability

to complete some types of rehabilitation. In this cohort of eight individuals, there were no serious episodes of autonomic dysregulation or dysreflexia that limited the intervention. While one individual experienced symptoms of an altered autonomic response, this response was likely unrelated to the addition of tsDCS; autonomic dysregulation occurred during both of his single sessions (tsDCS+LT and sham+LT) and had occurred previously during other walking interventions.

The assessment of tolerability also focused on how this combined intervention could potentially impact common post-SCI impairments. First, post-injury changes in skin integrity are a serious concern [20, 39]. The use of the commercially available saline-soaked electrodes under the tight harness during the intervention appeared well-tolerated. Correct and secure electrode placement required close attention and frequent monitoring of electrode sites ensured skin integrity. Second, spasticity is a severe and limiting complication for participation in walking rehabilitation. It was therefore encouraging that fluctuations in spasticity during the study appeared unrelated to use of tsDCS.

Two other concerns in SCI walking rehabilitation are pain and changes in sensation. While participant 11 reported a burning sensation during tsDCS for the short bout it is applied in the sham protocol, it is reassuring that the intensity only required adjustment on one training day. Interestingly, this individual reported no issues when the stimulation was on for the full 30 minutes during the tsDCS+LT single session. Participant 02 reported an episode of foot pain that occurred between sessions. The participant characterized the episode as a positive event since he had not had any sensation below his injury before the study. He also reported beginning to feel his feet on the floor during the course of the intervention which he felt improved his ability to walk. These participant responses highlight the importance of close monitoring and ongoing investigation of this combinatorial intervention.

Walking Performance

The outcomes for walking speed following the 16-session training suggest a possible benefit from the addition of tsDCS; achievement of clinically meaningful improvements in walking speed after training were more consistent in the tsDCS+LT group, occurring in three out of four, compared to the sham+LT group (one of four). Evidence of walking changes specific to the addition of tsDCS cannot be determined definitively in this small cohort, but examination of individual subject characteristics and training responses may provide insight to guide future directions.

Individuals who demonstrated training-induced improvement in walking speed, compared to those who did not, had no apparent differences in baseline walking function, lower extremity motor scores or intensity of training completed. One factor that may have contributed to their positive outcomes was their ability to practice walking outside of the intervention as reported by two of the three who made gains in the tsDCS+LT group. Of note, one participant progressed during the study to start walking at home with the assist of his wife, whereas prior they were unable to safely do so. The other was already an independent ambulator and could implement his practice in everyday community ambulation. Interestingly, the sham+LT group also had two individuals who reported walking practice outside of the intervention (one who was previously independent and the

other reaching a new level of function), but only one demonstrated improved walking speed. Of note, while all participants had chronic SCIs, all four of the individuals demonstrating clinically meaningful gains in walking speed were less than three years post-injury. It is possible that the spinal circuits in less chronic injury are more amenable to intervention from LT or tsDCS. Therefore, the relative contributions of tsDCS, self-training, injury chronicity and other factors are currently difficult to separate in determining their greater responses to the training.

While the speed change outcomes are encouraging, less gains were evident in the 6-minute walk test outcomes. Greater gains in speed may be evident since increased speeds were used to promote intensive training and many training sessions involved walking bouts that were less than six minutes. It is also possible that a limited number of training sessions, the presence of non-responders and lack of sensitivity in the 6-minute walk test may have contributed [33, 40].

Future Directions

Prior to a large-scale clinical trial of tsDCS with LT, further examination of this approach is needed. In particular, a larger sample size will be necessary to accurately estimate variance in response and determine the sample size for a large clinical trial. However, due to numerous participant factors (e.g., injury severity, chronicity, baseline capacity), response heterogeneity may require targeted investigations of individuals with narrower injury and baseline characteristics. While this approach will limit study inclusion, and thereby challenge recruitment, it may enable initial determination of efficacy and study of individuals most likely to respond. One limitation of this pilot investigation is our lack of data on the feasibility of recruiting individuals post-SCI who would be eligible for this intervention from the general public; our recruitment procedures were targeted at individuals associated with our large rehabilitation health system and utilized pre-approved approaches for database and record screening. Additionally, since this investigation included a small sample, further verification of tolerance and safety of this approach is warranted. The unfavorable response in one individual suggests that some individuals may need to acclimate to the stimulation. Since the unfavorable response occurred with someone during the sham exposure, it is not clear how they would have responded to the 16-session active stimulation protocol. Furthermore, advancement of combined tsDCS with LT will benefit from improved understanding of the mechanisms underlying tsDCS and how combination with rehabilitation may enhance effects, as well as investigation of long-term effects.

Implication for Clinical Translation

There are many therapist-identified barriers encountered when translating research to the clinic, such as development of new habits and routine clinical procedures required to ensure efficient practice. Other factors may include device use or set-up complexity, limited potential application (appropriate for a small number of patients), increased costs, and equipment access. However, several factors may allow for a combined intervention of tsDCS and task-specific training to be implemented easily and quickly. tsDCS is non-invasive and can be delivered with relative ease. The stimulation devices are also relatively low-cost and commercially available. Furthermore, neuromuscular electrical stimulation during functional

rehabilitation, such as LT, is already a standard of clinical practice. tsDCS could also be combined with other types of rehabilitation, increasing its potential use and ease of integration into clinical practice. Finally, this study adds to prior research on tsDCS during a single session post-SCI [17] and an intervention protocol post-stroke [28] to demonstrate a lack of adverse responses or safety concerns.

Acknowledgements:

The authors would like to acknowledge the participants and their families for their time and dedication to SCI rehabilitation research.

Funding:

This work was supported by the REACT Center of NIH/NICHD [RFA-HD-15–010], Brooks-PHHP Research Collaboration, the NIH National Center for Medical Rehabilitation Research T32 Neuromuscular Plasticity Training Program [grant number T32HDO43730] and the NIH/NICHD K12 Rehabilitation Research Career Development Program [grant number HDO55929].

Data Availability:

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

References

1. Behrman AL, Harkema SJ (2007) Physical rehabilitation as an agent for recovery after spinal cord injury. Phys Med Rehabil Clin N Am 18:183–202, v [PubMed: 17543768]
2. Ferris DP, Gordon KE, Beres-Jones JA, Harkema SJ (2004) Muscle activation during unilateral stepping occurs in the nonstepping limb of humans with clinically complete spinal cord injury. Spinal Cord 42:14–23 [PubMed: 14713939]
3. McCrea DA, Rybak IA (2008) Organization of mammalian locomotor rhythm and pattern generation. Brain Res Rev 57:134–146 [PubMed: 17936363]
4. Beres-Jones JA, Harkema SJ (2004) The human spinal cord interprets velocity-dependent afferent input during stepping. Brain J Neurol 127:2232–2246
5. Harkema SJ, Hurley SL, Patel UK, Requejo PS, Dobkin BH, Edgerton VR, et al. (1997) Human lumbosacral spinal cord interprets loading during stepping. J Neurophysiol 77:797–811 [PubMed: 9065851]
6. O'Shea TM, Burda JE, Sofroniew MV (2017) Cell biology of spinal cord injury and repair. J Clin Invest 127:3259–3270 [PubMed: 28737515]
7. Morawietz C, Moffat F (2013) Effects of locomotor training after incomplete spinal cord injury: a systematic review. Arch Phys Med Rehabil 94:2297–2308 [PubMed: 23850614]
8. Harkema SJ (2008) Plasticity of interneuronal networks of the functionally isolated human spinal cord. Brain Res Rev 57:255–64 [PubMed: 18042493]
9. Morse LR, Field-Fote EC, Contreras-Vidal J, Noble-Haeusslein LJ, Rodreick M, Shields RK, et al. (2021) Meeting Proceedings for SCI 2020: Launching a Decade of Disruption in Spinal Cord Injury Research. J Neurotrauma 38:1251–1266 [PubMed: 33353467]
10. Gomes ED, Silva NA, Salgado AJ (2019) Combinatorial therapies for spinal cord injury: strategies to induce regeneration. Neural Regen Res 14:69–71 [PubMed: 30531075]
11. Griffin JM, Bradke F (2020) Therapeutic repair for spinal cord injury: combinatory approaches to address a multifaceted problem. EMBO Mol Med 12:e11505 [PubMed: 32090481]
12. Estes SP, Iddings JA, Field-Fote EC (2017) Priming Neural Circuits to Modulate Spinal Reflex Excitability. Front Neurol 8:17 [PubMed: 28217104]

13. Cogiamanian F, Vergari M, Schiaffi E, Marceglia S, Ardolino G, Barbieri S, et al. (2011) Transcutaneous spinal cord direct current stimulation inhibits the lower limb nociceptive flexion reflex in human beings. Pain 152:370–5 [PubMed: 21159430]
14. Lamy JC, Ho C, Badel A, Arrigo RT, Boakye M (2012) Modulation of soleus H reflex by spinal DC stimulation in humans. J Neurophysiol 108:906–14 [PubMed: 22623482]
15. Murray LM, Tahayori B, Knikou M (2018) Transspinal Direct Current Stimulation Produces Persistent Plasticity in Human Motor Pathways. Sci Rep 8:717 [PubMed: 29335430]
16. Winkler T, Hering P, Straube A (2010) Spinal DC stimulation in humans modulates post-activation depression of the H-reflex depending on current polarity. Clin Neurophysiol 121:957–61 [PubMed: 20153248]
17. Hubli M, Dietz V, Schrafl-Altermatt M, Bolliger M (2013) Modulation of spinal neuronal excitability by spinal direct currents and locomotion after spinal cord injury. Clin Neurophysiol 124:1187–95 [PubMed: 23415451]
18. Harkema SJ, Hillyer J, Schmidt-Read M, Ardolino E, Sisto SA, Behrman AL, et al. (2012) Locomotor training: as a treatment of spinal cord injury and in the progression of neurologic rehabilitation. Arch Phys Med Rehabil 93:1588–97 [PubMed: 22920456]
19. Roy RR, Harkema SJ, Edgerton VR (2012) Basic concepts of activity-based interventions for improved recovery of motor function after spinal cord injury. Arch Phys Med Rehabil 93:1487–97 [PubMed: 22920448]
20. Park JW, Seo CH, Han SH, Lee YG (2011) Sympathetic influence on biomechanical skin properties after spinal cord injury. Spinal Cord 49:236–243 [PubMed: 20856260]
21. Gray M, Black JM, Baharestani MM, Bliss DZ, Colwell JC, Goldberg M, et al. (2011) Moisture-associated skin damage: overview and pathophysiology. J Wound Ostomy Cont Nurs Off Publ Wound Ostomy Cont Nurses Soc 38:233–241
22. National Institute for Health Research Evaluation, Trials and Studies Coordination Centre (NETSCC) (2012) Glossary.
23. Estes S, Zarkou A, Hope JM, Suri C, Field-Fote EC (2021) Combined Transcutaneous Spinal Stimulation and Locomotor Training to Improve Walking Function and Reduce Spasticity in Subacute Spinal Cord Injury: A Randomized Study of Clinical Feasibility and Efficacy. J Clin Med 10:1167 [PubMed: 33799508]
24. McHugh LV, Miller AA, Leech KA, Salorio C, Martin RH (2020) Feasibility and utility of transcutaneous spinal cord stimulation combined with walking-based therapy for people with motor incomplete spinal cord injury. Spinal Cord Ser Cases 6:104
25. Megía García A, Serrano-Muñoz D, Taylor J, Avendaño-Coy J, Gómez-Soriano J (2020) Transcutaneous Spinal Cord Stimulation and Motor Rehabilitation in Spinal Cord Injury: A Systematic Review. Neurorehabil Neural Repair 34:3–12 [PubMed: 31858871]
26. Manson GA, Calvert JS, Ling J, Tychhon B, Ali A, Sayenko DG (2020) The relationship between maximum tolerance and motor activation during transcutaneous spinal stimulation is unaffected by the carrier frequency or vibration. Physiol Rep 8:e14397 [PubMed: 32170844]
27. Sayenko DG, Rath M, Ferguson AR, Burdick JW, Havton LA, Edgerton VR, et al. (2019) Self-Assisted Standing Enabled by Non-Invasive Spinal Stimulation after Spinal Cord Injury. J Neurotrauma 36:1435–1450 [PubMed: 30362876]
28. Awosika OO, Matthews S, Staggs EJ, Boyne P, Song X, Rizik BA, et al. (2020) Backward locomotor treadmill training combined with transcutaneous spinal direct current stimulation in stroke: a randomized pilot feasibility and safety study. Brain Commun 2:fcaa045 [PubMed: 32954299]
29. Parazzini M, Fiocchi S, Liorni I, Rossi E, Cogiamanian F, Vergari M, et al. (2014) Modeling the current density generated by transcutaneous spinal direct current stimulation (tsDCS). Clin Neurophysiol Off J Int Fed Clin Neurophysiol 125:2260–2270
30. Brazg G, Fahey M, Holleran CL, Connolly M, Woodward J, Hennessy PW, et al. (2017) Effects of Training Intensity on Locomotor Performance in Individuals With Chronic Spinal Cord Injury: A Randomized Crossover Study. Neurorehabil Neural Repair 31:944–954 [PubMed: 29081250]

31. Hornby TG, Reisman DS, Ward IG, Scheets PL, Miller A, Haddad D, et al. (2020) Clinical Practice Guideline to Improve Locomotor Function Following Chronic Stroke, Incomplete Spinal Cord Injury, and Brain Injury. J Neurol Phys Ther JNPT 44:49–100 [PubMed: 31834165]
32. Behrman AL, Lawless-Dixon AR, Davis SB, Bowden MG, Nair P, Phadke C, et al. (2005) Locomotor training progression and outcomes after incomplete spinal cord injury. Phys Ther 85:1356–71 [PubMed: 16305274]
33. Scivoletto G, Tamburella F, Laurenza L, Foti C, Ditunno JF, Molinari M (2011) Validity and reliability of the 10-m walk test and the 6-min walk test in spinal cord injury patients. Spinal Cord 49:736–740 [PubMed: 21221120]
34. Button KS, Ioannidis JPA, Mokrysz C, Nosek BA, Flint J, Robinson ESJ, et al. (2013) Power failure: why small sample size undermines the reliability of neuroscience. Nat Rev Neurosci 14:365–376 [PubMed: 23571845]
35. Musselman KE (2007) Clinical significance testing in rehabilitation research: what, why, and how? Phys Ther Rev 12:287–296
36. Forrest GF, Hutchinson K, Lorenz DJ, Buehner JJ, Vanhiel LR, Sisto SA, et al. (2014) Are the 10 meter and 6 minute walk tests redundant in patients with spinal cord injury? PloS One 9:e94108 [PubMed: 24788068]
37. Cha J, Heng C, Reinkensmeyer DJ, Roy RR, Edgerton VR, De Leon RD (2007) Locomotor ability in spinal rats is dependent on the amount of activity imposed on the hindlimbs during treadmill training. J Neurotrauma 24:1000–1012 [PubMed: 17600516]
38. Field-Fote EC, Roach KE (2011) Influence of a locomotor training approach on walking speed and distance in people with chronic spinal cord injury: a randomized clinical trial. Phys Ther 91:48–60 [PubMed: 21051593]
39. Thorfinn J, Sjöberg F, Sjöstrand L, Lidman D (2006) Perfusion of the skin of the buttocks in paraplegic and tetraplegic patients, and in healthy subjects after a short and long load. Scand J Plast Reconstr Surg Hand Surg 40:153–160 [PubMed: 16687335]
40. Smith AC, Knikou M (2016) A Review on Locomotor Training after Spinal Cord Injury: Reorganization of Spinal Neuronal Circuits and Recovery of Motor Function. Neural Plast 2016:1216258 [PubMed: 27293901]

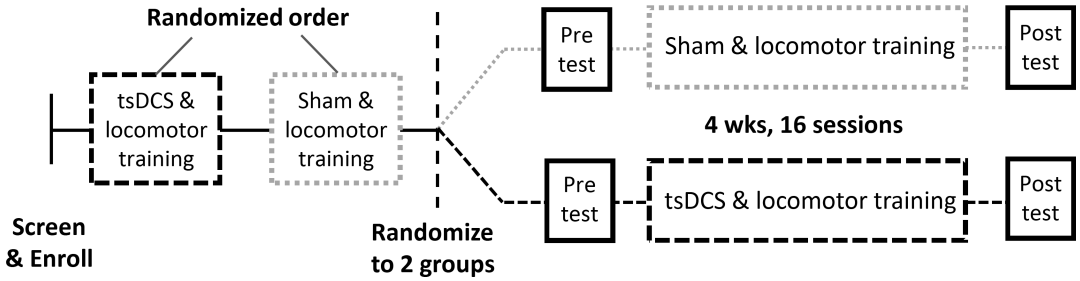

Figure 1.

Study procedures. Participants first completed two sessions in a random order of either tsDCS+LT or sham+LT where assessments were completed pre- and post-intervention in each session. Participants were then randomized to receive either tsDCS+LT or sham+LT for the 16-session training. Assessments were completed on a separate day before and after training.

Table 1.

Inclusion and exclusion criteria for study participation.

Inclusion criteria
1) age from 18 to 65 2) a single SCI (duration >1 year) classified as neurologic level T12 or above based on the International Standards for Neurological Classification of Spinal Cord Injury, and classified on the American Spinal Cord Injury Association (ASIA) Impairment Scale (AIS) as “C” or “D” motor incomplete at screening (Kirshblum et al., 2011) 3) capability of ambulating 3 meters with or without the use of gait devices, braces, or the assistance of one person 4) medical stability with no acute illness or infection 5) ability to provide informed consent
Exclusion criteria
1) current diagnosis of an additional neurologic condition (e.g., multiple sclerosis, Parkinson’s disease, stroke, or brain injury) 2) presence of unstable or uncontrolled medical conditions such as cardiovascular disease, myocardial infarction (<1 year), pulmonary infection or illness, renal disease, autonomic dysreflexia, infections, pain, heterotopic ossification 3) cognitive or communication impairments limiting communication with study staff or ability to provide informed consent 4) lower extremity joint contractures, pain, skin lesions/wounds, severe spasticity/uncontrolled movements or an acute or unstable fracture, diagnosis of osteoarthritis or bone impairments affecting participation in walking rehabilitation 5) body weight or height that is incompatible with safe use of a support harness and body weight support system 6) current participation in rehabilitation to address walking function 7) botox injections in lower extremity muscles affecting walking function within 4 months of study enrollment 8) legal blindness or severe visual impairment 9) known pregnancy 10) implanted metal hardware of the spine below the 8th thoracic vertebrae.

Table 2.

Participant demographics. AIS and Lower Extremity Motor Score were determined using the International Standards for Neurological Classification of Spinal Cord Injury completed at the pre-training assessment.

Participant number	Training group	Age	AIS	Months post-injury	Lower Extremity Motor Score	Walking speed (m/s)	Ambulatory status
01	tsDCS+LT	33	C1, D	27	Left: 18/25 Right: 20/25	0.83	Community ambulator No assistive device
02	tsDCS+LT	61	C1, C	21	Left: 0/25 Right: 5/25	0.13	Power wheelchair user
03	tsDCS+LT	58	T3, D	89	Left: 15/25 Right: 19/25	0.16	Manual wheelchair user
06	Sham+LT	62	C1, D	63	Left: 14/25 Right: 11/25	0.14	Ambulates with caregiver assist (grip deficits limit device use)
08	Sham+LT	31	C6, D	101	Left: 15/25 Right: 13/25	0.07	Manual wheelchair user
09	tsDCS+LT	59	C1,D	20	Left: 7/25 Right: 25/25	0.14	Power wheelchair user
10	Sham+LT	60	T7, D	486	Left: 25/25 Right: 18/25	0.59	Community ambulatory with walking stick
11	Sham+LT	52	T1, D	12	Left: 14/25 Right: 25/25	0.28	Manual wheelchair user
tsDCS+LT group average		**52.8**		**39.3**	**27.8/50**	**0.32**	
Sham+LT group average		**51.3**		**165.5**	**34.0/50**	**0.27**	

Abbreviations: AIS - American Spinal Injury Association (ASIA) Impairment Scale; m/s – meters per second

Table 3.

Average intensity indicators during training for each participant and by group.

	OG RPE	TM RPE	TM Peak HR	% of HR max	TM speed (m/s)	% increase in training TM speed	Estimated steps
tsDCS+LT							
01	N/A	15.9	119.4	65	2.6	63	2826
02	18.5	18.3	100.1	61	0.9	125	1563
03	17.6	15.7	117.9	71	1.1	83	1280
09	18.8	17.6	109.5	68	1.1	57	2117
Average(SD)	**18.3(0.6)**	**16.9(1.3)**	**111.7(8.9)**	**66.3(4.3)**	**0.6(0.4)**	**82(31)**	**1947(682)**
Sham+LT							
06	13	11.9	129.9	79	1.0	100	1298
08	15.5	16.8	123.4	66	0.6	20	806
10	13.4	13.1	118.2	74	1.6	33	1765
11	16.5	14.9	95.2	57	1.5	67	1469
Average(SD)	**14.6(1.7)**	**14.2(2.1)**	**116.7(15.1)**	**69.0(9.6)**	**0.5(0.2)**	**55(36)**	**1335(402)**

Abbreviations: RPE – rate of perceived exertion; OG – overground; TM – treadmill; HR – heart rate; tsDCS – transcutaneous spinal direct current stimulation; LT – locomotor training; sham – sham tsDCS; m/s – meters per second

Table 4.

Change in walking function outcomes after 16-session training.

	01	02	03	09	tsDCS + LT	06	08	10	11	Sham + LT
10 MWT (m/s)	40%	43%	−26%	84%	**35(46)%**	−19%	−27%	−30%	50%	**−7(38)%**
	0.60	0.06	−0.08	0.15	**0.18(.29)**	−0.07	−0.05	−0.33	0.24	**−0.05(.23)**
6 MWT (m)	41%	−3%	−15%	25%	**12(26)%**	−16%	64%	−24%	130%	**39(73)%**
	(139.3)	(−1.1)	(−4.9)	(12.4)	**36.4(69.0)**	(−7.7)	(22.6)	(−65.7)	(70.2)	**4.9(56.9)**

Abbreviations: 10 MWT – 10-meter walk test; 6 MWT – 6-minute walk test.