

Transcutaneous spinal cord stimulation plus locomotor training versus sham-stimulation plus locomotor training in chronic spinal cord injury (eWALK): a multicentre, triple-blind, randomised, sham-controlled trial



Elizabeth A. Bye,^{a,b,p} Claire L. Boswell-Ruys,^{a,b,p} Martin E. Héroux,^{a,b} Bonsan B. Lee,^{a,b,c} Euan J. McCaughey,^{a,b,d} Zoë J. Djajadikarta,^{a,b} Monica A. Perez,^{e,f,g} Gabrielle Mendoza,^{e,f} Margaret Purcell,^d Claire Lincoln,^d Julian Taylor,^{h,i,j} Marta Ríos-León,^{h,j} Gavin Williams,^{k,l} Matt Kundevski,^{k,m} Joanna Diong,^{a,n} Peter Humburg,^b Bing Chen,^e Nadine Fuchs,^a Harrison Finn,^{a,o} Raquel Menchero,^h Ramiro Palazón-García,^h Sabrina Sepúlveda-Rodríguez,^h Scott Starkey,^m Terry Trinh,^{a,b} Jane E. Butler,^{a,b,q,r,s} and Simon C. Gandevia^{a,b,*q,r,s}



^aNeuroscience Research Australia, Sydney, NSW, Australia

^bUniversity of New South Wales, Sydney, NSW, Australia

^cPrince of Wales Hospital, Sydney, NSW, Australia

^dQueen Elizabeth National Spinal Injuries Unit, Queen Elizabeth University Hospital, Glasgow, Scotland

^eShirley Ryan Ability Lab, Chicago, USA

^fEdward Hines J, Jr. VA Hospital, IL, USA

^gDepartment of Physical Medicine and Rehabilitation, Northwestern University, Chicago, USA

^hHospital Nacional de Paraplégicos (SESCAM), Toledo, Spain

ⁱHarris Manchester College, University of Oxford, UK

^jInstituto de Investigación Sanitaria de Castilla-La Mancha (IDISCAM), Toledo, Spain

^kEpworth HealthCare, Melbourne, Australia

^lUniversity of Melbourne, Melbourne, VIC, Australia

^mSwinburne University of Technology, Melbourne, VIC, Australia

ⁿUniversity of Sydney, Sydney, Australia

^oUniversity of Utah, Salt Lake City, USA

Summary

Background Although some studies have investigated the effects of transcutaneous spinal cord stimulation (tSCS), most are small, uncontrolled, and exploratory. We aimed to determine whether 12 weeks of tSCS combined with locomotor training improves walking ability (with stimulation) in people with chronic spinal cord injury (SCI) more than locomotor training alone.

Methods This international, multicentre, triple-blind, randomised sham-controlled trial (eWALK) was conducted at seven sites across Australia, USA, Scotland, and Spain. We recruited 50 community-dwelling individuals (aged ≥16 years) with chronic SCI, motor levels T1-T11 as per the International Standards for the Neurological Classification of SCI (ISNCSCI), and limited walking ability (Walking Index for SCI II (WISCI-II) levels 1–6). Participants were randomly assigned (1:1) to the stimulation or sham-stimulation group. Participants received their allocated stimulation plus locomotor training for three 30-min sessions a week for 12 weeks. Participants, assessors, and therapists providing training were unaware of group allocation. The primary outcome was walking ability (WISCI-II) with allocated stimulation at 12 weeks. A predefined between-group difference of 2 points on the WISCI-II was set as the minimally worthwhile (ie, clinically meaningful) treatment effect. Outcomes were measured at baseline, Week 12, and, Week 16 (follow-up). Adverse events were recorded across the 12-week training period. Multiple imputation was used to impute missing values. This trial is registered with ANZCTR.org.au, ACTRN12620001241921.

Findings Between March 10, 2021, and June 14, 2024, 50 participants were enrolled and randomly allocated to study groups (stimulation group n = 25; sham-stimulation group n = 25). Data from all 50 participants were included in the

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*Corresponding author. Kolling Institute, 10 Westbourne Street, St Leonards, NSW 2065, Australia.

E-mail address: simon@gandeviaresearch.com (S.C. Gandevia).

^pJoint first authorship.

^qJoint senior authorship.

^rCurrent affiliation: Kolling Institute, Sydney, NSW, Australia.

^sCurrent affiliation: University of Sydney, Sydney, NSW, Australia

primary analysis (including two dropouts). The mean between-group difference (95% CI) for walking ability with stimulation was -0.1 out of 20 on the WISCI-II (-1.6 to 1.5 ; $p = 0.98$) at 12 weeks, which did not meet the predefined clinically meaningful treatment effect of 2 points. Both groups showed improvements in walking ability with and without allocated stimulation at 12 weeks, which was maintained at 16 weeks. The number of adverse events reported was similar across groups (72 in the stimulation group, 50 in the sham group). The most frequent were skin abrasion/pressure area ($n = 23$), urinary incontinence ($n = 11$), and musculoskeletal pain ($n = 10$). There were no serious adverse events.

Interpretation Our findings show that 12 weeks of tSCS plus locomotor training did not improve walking for people with chronic SCI and limited walking ability, more than 12 weeks of locomotor training alone did. Future research could investigate the effects of tSCS across diverse SCI populations, such as individuals with cervical injuries, and assess its potential when combined with upper limb training or locomotor training in those with greater mobility.

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Keywords: Neuromodulation; Non-invasive spinal cord stimulation; Transcutaneous spinal cord stimulation; Locomotor training; Spinal cord injury

Research in context

Evidence before this study

Transcutaneous spinal cord stimulation (tSCS) has generated growing interest as a rehabilitation intervention for individuals with spinal cord injury (SCI), with promising preliminary reports. Before conducting this trial, we searched PubMed for clinical trials published, with no language restrictions, between database inception and June 4, 2020. The search terms included “transcutaneous spinal stimulation”, “neuromodulation”, “spinal cord injury”, “non-invasive” “motor”, and “locomotor”. No randomised controlled trials (RCTs) evaluating tSCS combined with motor training in people with SCI were identified. A systematic review published in 2020 concluded that the evidence for the efficacy of non-invasive spinal stimulation was inconclusive. The review stated that existing studies were limited by small sample sizes and highlighted the need for well-designed RCTs to rigorously assess the effectiveness

of tSCS for motor rehabilitation following SCI. We aimed to address this knowledge gap.

Added value of this study

To the best of our knowledge, this randomised sham-controlled trial is the first to assess the effects of tSCS combined with locomotor training in patients with chronic SCI. The results, from 50 participants, demonstrate that tSCS combined with a 12-week locomotor training programme did not improve walking more than locomotor training alone.

Implications of all the available evidence

This study, combined with a recent RCT in subacute SCI (Comino-Suárez et al.), provides evidence that tSCS does not further improve walking beyond locomotor training alone. Future studies could investigate tSCS in a broader population with SCI and a wider range of stimulation protocols.

Introduction

Spinal cord injury (SCI) can lead to widespread paralysis that affects a person's ability to walk. Regaining this ability is a priority for these individuals.¹ Although locomotor training is a common approach to improve walking, evidence for its effectiveness is limited² with no approach being superior.³ Given the growing view that multi-modal approaches lead to better outcomes in SCI,⁴ transcutaneous spinal cord stimulation (tSCS) combined with locomotor training has gained considerable interest, with promising preliminary reports.^{5–7}

It is believed that tSCS activates dorsal roots at the level of stimulation to reflexly excite spinal motoneurons.

It has also been proposed that tSCS may activate cutaneous afferent fibres over the back muscles. Notably, a case study reported reductions in hypertonus when electrodes were positioned 10 cm lateral to the spinal column.⁸ Stimulation below the level of injury can increase the effectiveness of spared descending connections that cross the lesion site.⁹ As locomotor training relies on voluntary effort and afferent input to generate rhythmic motor output,¹⁰ it is hypothesised that combined tSCS and locomotor training may further improve walking.¹¹

Two recent systematic reviews^{12,13} highlight the lack of randomisation, blinding, sham stimulation and reporting on recruitment among studies investigating

tSCS. Placebo effects are also a problem in trials using spinal cord stimulation.^{14,15} Moreover, the majority of studies have relatively small sample sizes. Thus, there is limited evidence for the efficacy of tSCS. Indeed, a recent randomised, double-blind, sham-controlled clinical trial in 27 participants showed no improvements in walking after 20 sessions of tSCS plus locomotor training, although 1 month later improvements were evident without further tSCS.¹⁶

Standardised protocols to determine stimulation intensities are also lacking.¹⁷ A common approach for setting stimulation intensity uses subjective criteria, such as participant tolerance or paraesthesia.¹⁸ This approach is problematic due to differences in injury severity and sensory deficits, which result in intensities that are not comparable across participants. Other studies have addressed this with the use of objective neurophysiological criteria; specifically, the lowest single-pulse stimulation intensity to elicit a spinally-evoked motor response (sEMR).¹⁹

To date, a paucity of evidence and the absence of standardised protocols has hindered translation of tSCS into clinical practice. This study aimed to determine if 12 weeks of combined tSCS and locomotor training improves walking, lower limb strength,^{20,21} spasticity, sensation,^{22,23} bowel function^{23,24} and quality of life. We compared tSCS plus locomotor training with sham tSCS plus locomotor training in this high-quality randomised, triple-blind, sham-controlled clinical trial.

Methods

Study design

A prospective international multicentred, randomised, triple-blinded, sham-controlled clinical trial was conducted across seven sites: one research institute in Australia (Sydney), one university (Melbourne, Australia) and five hospitals/clinics (USA, Scotland and Spain). The first and last participants were randomised in March 2021 and June 2024.

The trial was performed in accordance with the principles of the Declaration of Helsinki and is reported in line with the Consolidated Standards of Reporting Trials (CONSORT) statement for clinical trials. Full study details can be found in the trial protocol and statistical analysis plan (see [Supplementary Material](#)). The trial was prospectively registered on Nov 20, 2020 at Australian New Zealand Clinical Trial Registry (ACTRN12620001241921) and Universal Trial Number (U1111-1251-9618).

Ethics

Each site obtained approval from institutional review and ethics boards before trial initiation. The main ethics approval was provided by the University of New South Wales Human Research Committee (HC200478). Written consent was obtained from participants prior to enrolment.

Participants

Eligible individuals with chronic SCI were recruited from the community through existing research databases, referrals from health professionals, and advertisements on websites of SCI organisations. Participants were included if they were more than 16 years of age, had sustained a SCI at least 12 months before consent, had bilateral motor levels between T1 and T11 (International Standards for the Neurological Classification of SCI, ISNCSCI), had a Walking Index for Spinal Cord Injury II (WISCI-II) between level 1 and 6, had a reproducible, voluntary muscle contraction in at least one lower limb muscle group, and were considered by their spinal physician to be able to undertake and complete the trial. Full inclusion and exclusion criteria have been published.²⁵ Metal hardware under the site of stimulation was removed from the exclusion criteria after enrolling 21 participants.

Randomisation and masking

Participants were randomised to one of two groups: the stimulation group or the sham-stimulation group. A secure blocked random-allocation schedule was computer-generated prior to the start of the trial by an independent person not directly involved in the trial. The random-allocation schedule consisted of 50 three-digit codes: 25 assigned to the stimulation group and 25 assigned to the sham-stimulation group. The three-digit codes were used to programme the stimulator control unit. The random-allocation schedule was uploaded to REDCap to allow each site to randomise participants.

As for masking, this was a triple-blind trial. Participants, assessors, and, therapists providing training were unaware of group allocation. The experimental set-up, procedures, and training were identical for participants randomised to the sham group, except for stimulation intensity. Stimulation parameters were concealed throughout the training sessions to maintain blinding for participants and trainers. Assessors were not involved in training participants.

Intervention

Locomotor training

Both groups received three 30-min locomotor training sessions per week for 12 weeks while receiving their allocated stimulation.²⁵ The 30-min consisted solely of active participation in standing or walking exercises, with set-up time excluded. Participants underwent five treadmill and one overground training session(s) every 14 days. Training was delivered by experienced physical therapists. Therapists received mandatory training in how to perform the training. The details of each training session were recorded by the therapist in a training diary including the number of sessions attended and missed.

Transcutaneous spinal stimulation

The stimulation has been fully described elsewhere.²⁵ Stimulation was delivered at 20 Hz (10 kHz burst-modulated, biphasic 1 ms-pulses; DS8R, Digitimer, UK) driven by a custom stimulator control unit with the upper portion of the cathode (5 × 10 cm) aligned with the L1-L2 vertebral interspace and anode (5 × 10 cm) oriented horizontally over the abdomen. The stimulator control unit controlled the DS8R to deliver either stimulation or sham-stimulation. Stimulation parameters were concealed throughout the training sessions to maintain blinding for participants and trainers. Threshold intensity was defined as the lowest single pulse intensity that evoked sEMR in the vastus medialis. This threshold was assessed prior to randomisation and then re-assessed every 2 weeks, during the training period. The intensity used at Week 10 of the training programme was used during the Week 12 and 16 assessments.

Sham transcutaneous spinal stimulation

Sham stimulation started at 50% of threshold intensity for 30s, then decayed to 0 mA over 30s. Occasionally during training participants were exposed to an additional 30 s of stimulation at 50% of threshold following a rest in a chair. Participants, therapists and assessors were blinded to group allocation.

A standard script indicating that sensory and muscles responses may adapt to stimulation was read to all participants prior to their first training session. Thus, participants with sensation at the site of stimulation were not surprised if perceived stimulation intensity decreased over time. Participants were also instructed not to speculate about their group allocation with therapists or assessors.

Outcomes

Primary and secondary outcomes were selected based on a review of previous studies investigating the benefits of locomotor training or tSCS in people with SCI. Participants were assessed on three occasions by independent physiotherapists trained in the assessments. No assessor reported becoming unblinded. At Week 12, assessors reported the perceived allocation of the participant. Participants were assessed once prior to randomisation (baseline), once after 12 weeks of training, and once 4 weeks after completion of all training sessions (Week 16). At weeks 12 and 16, the primary outcome and all secondary outcomes (except sensation, bowel function and quality of life) were assessed twice, once with and once without the allocated stimulation with the order randomised across participants and assessment times. This design allowed us to explore two potential mechanisms; whether stimulation enhances the effect of training over time (i.e. benefits persist even when stimulation is off) or whether tSCS exerts an immediate effect that becomes

more pronounced with continued training but still requires stimulation to be on, to act similar to a prosthetic. Outcomes are outlined below and full details of all outcomes can be found in the published protocol (also available in [Supplementary Material](#)).²⁵

Primary outcome

The primary outcome was walking ability with allocated stimulation at 12 weeks. Walking ability was assessed with the WISCI-II (score out of 20). Before the start of the study, a predefined between-group difference of 2 points was set as the minimally clinically meaningful and worthwhile treatment effect.²⁶

Secondary outcomes

Secondary outcomes were as follows. Walking ability with allocated stimulation at 16 weeks assessed with the WISCI-II. All other secondary outcomes were assessed at 12 and 16 weeks. Walking ability without allocated stimulation assessed with the WISCI-II. Lower extremity motor function with and without allocated stimulation assessed with the Lower Extremity Motor Score (LEMS) from the ISNCSCI²⁷ (score out of 50). Lower limb spasticity with and without allocated stimulation assessed bilaterally with the Modified Ashworth Scale²⁸ in knee extensors, ankle plantar flexors, and hip flexors (score out of 30). Sensation without allocated stimulation assessed with the sensory score of the ISNCSCI²⁷ (score out of 224). Bowel function assessed with the Neurogenic Bowel Dysfunction questionnaire²⁹ (score out of 47). Quality of life assessed using the EuroQol-5 Dimension-5 Level questionnaire (EQ-5D-5L)³⁰ and a visual analogue scale out of 100.

Additional outcomes

Masking outcomes. After the Week 12 assessment, participants reported if they had been unblinded and their perceived group allocation to gauge blinding success). The therapists providing the training also reported the perceived allocation of the participant. Participants also rated the training programme on an 8-point scale, where 0 indicated “not worthwhile” and 7 indicated “extremely worthwhile”.

Safety outcomes. All adverse events (AEs) whether related or unrelated to the intervention, were recorded in the training diary for each participant throughout the 12-week training period and during all assessments at Weeks 12 and 16, but not during the 1-month of no training. At the start of each training session, the therapist routinely asked participants whether they had experienced any AEs since the previous session. Investigators used clinical judgement to determine their severity, cause, and expectedness.³¹ Expectedness was determined by whether the AE event was consistent with risks associated with tSCS that were specified in

the trial protocol, such as pressure injuries and autonomic dysreflexia.

Additional safety data were collected during all training sessions, including mandatory blood pressure measurements and scheduled skin checks. During the first two weeks, blood pressure was obtained, via a sphygmomanometer, recorded at the start of each session and at 5, 15 and 30 min of stimulation. After this initial period, the 5-min check was discontinued, while all other measurements continued. Skin checks focused on the electrode sites and contact points of the body-weight support harness and were performed at the same time-points as the blood pressure measurements.

Statistical analysis

A priori sample size calculations indicated that 50 participants would give >90% probability of detecting a between-group difference of 2 points (SD 2 points)^{32,33} on the primary outcome ($\alpha = 0.05$, dropout rate 15%).

De-identified data were collected in paper format using case report forms and entered into a secure electronic data management system (REDCap) hosted by Neuroscience Research Australia (NeuRA). Data were entered twice by independent investigators to minimise data entry errors.

The trial was overseen by a Safety and Data Monitoring Committee and an independent trial monitor. The committee was responsible for safeguarding participant interests and ensuring the integrity of the trial. Its role included monitoring the safety and efficacy of the intervention. The committee met approximately every six months throughout the study to conduct unblinded safety analyses to assess the balance of adverse events across the two groups. The independent trial monitor ensured data quality and checked compliance with the trial protocol via online sessions with each site.

Primary and secondary outcomes were analysed under an intention-to-treat framework with prespecified linear mixed-effects models with random intercepts for participants. This approach appropriately accounts for within-participant correlation arising from repeated measures and allows inclusion of all available data without listwise deletion. Fixed effects included group, time, and their interaction. Model assumptions were evaluated by inspection of residuals. For all outcomes, the treatment effect was the difference in means between the stimulation and sham groups (i.e. mean outcome of stimulation group minus mean outcome of sham group).

Participants with incomplete measurements were included, and multiple imputation was used to impute missing outcomes and covariates. Candidate predictors included the registered primary and secondary outcomes at all time points, and additional baseline variables (age, neurological level, American Spinal Injuries Association Impairment Scale (AIS), time since injury). Multiple imputation using chained equations was

performed by predictive mean matching (using 5 nearest neighbours) to generate 20 imputed datasets. Model coefficients from imputed datasets were pooled using Rubin's rules to obtain mean between-group differences and 95% confidence intervals (CI) at 12 and 16 weeks. Post-hoc analysis examined walking ability with and without stimulation over time, pooled across groups. An additional suggested post-hoc constrained baseline analysis³⁴ examined the primary outcome.

Sensitivity analyses were performed by re-running the models without imputations of missing values to assess the robustness of the findings (Table 1 in [Supplementary Material](#)).

We intended to obtain the mean effect of stimulation on participants who adhered to the randomised treatment regardless of group allocation. However, as adherence to treatment was high (median (IQR) of 33 (31–36) sessions attended), we elected not to perform this analysis and restrict the number of tests.

All effects were estimated with 95% CI and all statistical tests were 2-sided with an α level of 0.05. Findings from analyses of secondary outcomes, including Week 12 to Week 16 contrasts, are regarded as exploratory. The analysis plan is available in [Supplementary Material](#). Statistical analysis was conducted blinded using Stata v18 (StataCorp) and validated by a biostatistician.

Role of funding source

The funding bodies had no role in the study design, data collection, data analysis, data interpretation, writing of the report, or decision to submit the manuscript for publication.

Results

Between March 10, 2021 and June 14, 2024, 529 participants with SCI were assessed for eligibility; of whom 479 were deemed ineligible and excluded, with 50 participants ultimately enrolled and randomly assigned to either stimulation or sham-stimulation. [Fig. 1](#) shows flow of participants through the trial and reasons for exclusion. [Table 1](#) shows participant characteristics. The groups were similar at baseline for key prognostic factors.

There was no effect of combined tSCS and locomotor training on the primary outcome of walking, compared to locomotor training alone ([Table 2](#)). The mean between-group difference for walking while receiving allocated stimulation at 12 weeks was -0.1 (95% CI, -1.6 to 1.5 ; $p = 0.98$) out of 20 where a positive effect favours the stimulation group. The constrained baseline analysis effect was -0.4 (95% CI -1.8 to 1.0). [Fig. 2](#) shows individual and group data for the primary outcome. There was no effect of treatment on any secondary outcome at 12 and 16 weeks ([Table 2](#)). The

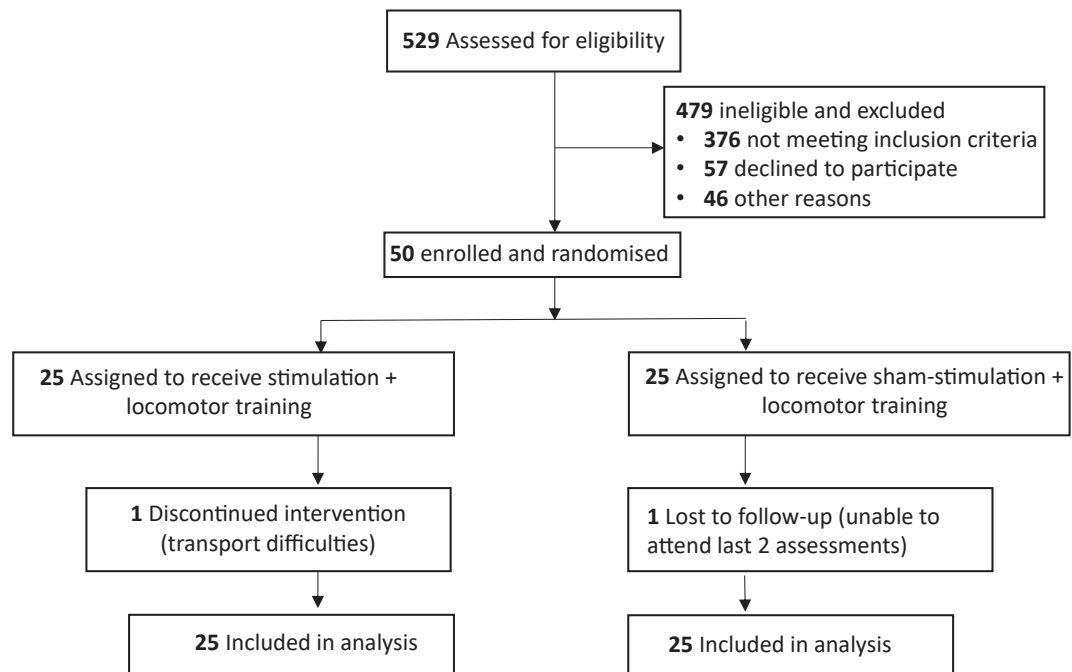


Fig. 1: Trial profile.

results for individual and group data for walking ability, motor score, and spasticity, all with and without allocated stimulation are shown in [Fig. 1](#) in [Supplementary Material](#).

	Stimulation Group (n = 25)	Sham group (n = 25)
Age (years), median (IQR)	46 (37–56)	38 (26–45)
Sex ^a (F:M, n)	5:20	5:20
Lower limb motor score (/50 points), mean (SD) ^b	12.8 (13.1)	14.3 (14.1)
Time since injury (years), median (IQR)	4 (2–8)	3 (2–6)
Neurological level, n ^b		
C7-T5	11	14
T6-T11	14	11
AIS classification, n ^b		
A	4	1
B	0	0
C	16	17
D	5	7
Motor level, n ^b		
T1-5	11	15
T6-11	14	10
Sensory level, n ^b		
C7-T5	11	15
T6-T11	14	10
WISCI-II, median (IQR)	1 (1–3)	3 (1–6)

Abbreviations: IQR, interquartile range; AIS, American Spinal Injuries Association. Impairment Scale, WISCI-II, Walking Index for Spinal Cord Injury II. ^aSex was assessed by participant self-report. ^bBased on the International Standards for the Neurological Classification of SCI.

Table 1: Characteristics of participants.

Walking ability improved over time in both groups (WISCI-II with allocated stimulation at Week 12: 2.5, 95% CI 1.7–3.3, $p < 0.001$; WISCI-II without allocated stimulation at Week 12: 2.5, 95% CI 1.7–3.3, $p < 0.001$). This improvement was maintained at Week 16 ([Fig. 2](#)).

The participants' perception of the training programme (median (IQR)) was 7.0 (5.5–7.0) for the stimulation group and 7.0 (6.5–7.0) for the sham group, where a score of 7 indicates “extremely worthwhile”.

All assessors and participants remained unaware of treatment allocation (i.e. blinded). 21 therapists were unblinded, with 12/50 participants having an unblinded therapist for some sessions. The most common reason for unblinding was inadvertent disconnection of stimulator leads that activated an alarm indicating impedance was too high. This occurred only in participants allocated to the stimulation group. The other reason for therapist unblinding was accidental contact with an active electrode, resulting in a mild electric shock.

Assessors and participants reported perceived group allocation ([Table 3](#)). Some participants in the stimulation group mistakenly thought they were in the sham group and vice versa.

Regarding safety, there were no serious adverse events. 122 AEs (72 stimulation group, 50 sham group) were recorded over the 12-week training period. The most frequent were skin abrasion/pressure area ($n = 23$), urinary incontinence ($n = 11$), and musculo-skeletal pain ($n = 10$). A full list of all AEs reported across the study is available within [Table 2](#) of the [Supplementary Material](#).

Outcomes	Baseline		Week 12		Week 16		Between-group mean difference (95% CI) baseline to week 12	Between-group mean difference (95% CI) baseline to week 16	Between-group mean difference (95% CI) week 12–week 16
	Stimulation	Sham	Stimulation	Sham	Stimulation	Sham			
Walking ability with stimulation, WISCI-II score (/20)	2.4 (1.9) n = 25	3.2 (2.2) n = 25	4.9 (3.7) n = 24	5.8 (3.5) n = 24	5.5 (3.6) n = 21	6.0 (3.4) n = 22	−0.1 (−1.6 to 1.5) p = 0.94	0.2 (−1.3 to 1.8) p = 0.76	0.3 (−1.3 to 1.9) p = 0.71
Walking ability without stimulation/sham, WISCI-II score (/20)	2.4 (1.9) n = 25	3.2 (2.2) n = 25	4.8 (3.7) n = 24	5.8 (3.5) n = 24	4.8 (3.9) n = 22	5.9 (3.4) n = 21	−0.2 (−1.9 to 1.5) p = 0.82	−0.5 (−2.2 to 1.3) p = 0.58	−0.3 (−2.1 to 1.5) p = 0.75
Lower limb motor function with stimulation/sham, LE motor score (/50)	12.8 (13.1) n = 25	14.3 (14.1) n = 25	14.8 (12.7) n = 24	15.4 (14.0) n = 24	15.9 (13.4) n = 22	16.0 (13.9) n = 23	0.0 (−2.4 to 2.4) p = 0.99	0.4 (−2.3 to 3.1) p = 0.78	0.4 (−2.2 to 3.0) p = 0.77
Lower limb motor function without stimulation/sham, LE motor score (/50)	12.8 (13.1) n = 25	14.3 (14.1) n = 25	14.8 (12.6) n = 24	15.1 (13.7) n = 24	15.5 (13.1) n = 22	15.3 (14.0) n = 23	0.3 (−2.4 to 3.0) p = 0.83	1.3 (−1.8 to 4.4) p = 0.42	1.0 (−2.1 to 4.0) p = 0.53
Spasticity with stimulation/sham Modified Ashworth scale (/30)	6.8 (5.6) n = 25	6.9 (3.7) n = 25	7.3 (6.0) n = 24	6.5 (3.6) n = 24	6.8 (5.9) n = 22	6.7 (3.4) n = 23	0.7 (−1.5 to 2.9) p = 0.54	0.5 (−1.8 to 2.7) p = 0.68	−0.2 (−2.5 to 2.1) p = 0.85
Spasticity without stimulation/sham Modified Ashworth Scale (/30)	6.8 (5.6) n = 25	6.9 (3.7) n = 25	7.8 (6.2) n = 24	6.2 (3.9) n = 24	5.6 (4.8) n = 22	6.6 (3.3) n = 23	1.4 (−0.8 to 3.6) p = 0.20	−0.5 (−2.7 to 1.8) p = 0.68	−1.9 (−4.2 to 0.4) p = 0.11
Sensation without stimulation/sham, Sensory score (/112)	130.6 (28.6) n = 25	128.8 (27.5) n = 25	134.9 (26.1) n = 23	131.3 (24.5) n = 24	134.7 (30.8) n = 21	133.1 (26.2) n = 22	−0.6 (−9.5 to 8.4) p = 0.90	1.6 (−7.8 to 11.0) p = 0.74	2.2 (−7.4 to 11.7) p = 0.66
Bowel function, Neurogenic Bowel Dysfunction score (/47)	10.3 (4.6) n = 24	12.3 (5.8) n = 24	10.1 (3.4) n = 23	11.5 (4.3) n = 23	9.5 (4.4) n = 21	11.4 (6.3) n = 22	1.1 (−1.6 to 3.7) p = 0.42	0.4 (−2.4 to 3.1) p = 0.80	−0.7 (−3.5 to 2.0) p = 0.61
Quality of life, EQ-5D-5L questionnaire Index (/1)	0.5 (0.2) n = 25	0.5 (0.2) n = 25	0.4 (0.2) n = 24	0.5 (0.2) n = 24	0.4 (0.2) n = 22	0.5 (0.3) n = 23	0.0 (−0.1 to 0.1) p = 0.91	0.0 (−0.1 to 0.1) p = 0.76	0.0 (−0.1 to 0.1) p = 0.85
Quality of Life, EQ-5D-5L VAS (/100)	76.6 (13.7) n = 25	79.8 (16.4) n = 25	71.8 (17.4) n = 24	76.3 (21.6) n = 24	73.1 (20.5) n = 22	73.9 (22.2) n = 23	−1.6 (−10.1 to 6.9) p = 0.71	3.8 (−5.0 to 12.5) p = 0.40	5.4 (−3.3 to 14.0) p = 0.22

Abbreviations: WISCI-II, Walking Index for Spinal Cord Injury II, LE, lower extremity, EQ-5D-5L, EuroQol-5 Dimension-5 Level questionnaire, VAS, Visual Analogue Scale. Mean (SD) summary statistics of observed data, and mean (95% CI) between group differences, at follow-up relative to baseline by intention-to-treat (ITT), estimated using multiple imputation. Within group sample sizes n indicate number of participants before missing values are imputed.

Table 2: Primary outcome and secondary outcomes.

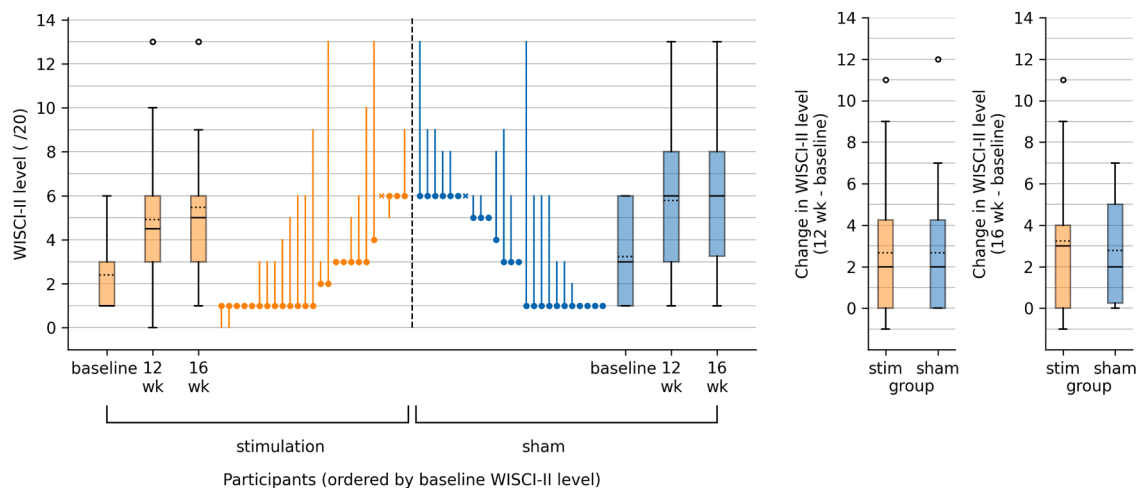


Fig. 2: Changes in 12-week and 16-week WISCI-II level assessed with allocated stimulation in participants treated with stimulation versus sham. Baseline walking ability on the Walking Index for Spinal Cord Injury II with allocated stimulation (WISCI-II; score range, 0–20; 0 = Client is unable to stand and/or participate in assisted walking; 20 = Ambulates with no devices, no braces and no physical assistance, 10 m; minimal clinically important difference = 2). Data are shown in ascending order for the stimulation group and in descending order for the sham group. Lines connect each participant's baseline WISCI-II level to their 12-week follow-up WISCI-II level. An x indicates participants with a baseline level but no 12-week level. The box plots show the distribution of baseline and follow-up (12-week and 16-week) WISCI-II levels for each group. In the right panels, box plots for each treatment group show the distribution of changes in WISCI-II level from baseline to 12 weeks, and from baseline to 16 weeks, excluding participants with missing follow-up data. Each box spans the IQR, with the median shown as a solid line and the mean shown as a dashed line. Whiskers extend to the most extreme value within 1.5 times the IQR, and open circles represent individual data points outside this range.

Two participants dropped out of the trial; one after three training sessions due to transportation difficulties and declined all assessments, and the other following an unrelated fall that prevented them from attending the Week 12 and 16 assessments. Participants in the stimulation group received a median (IQR) of 35 (32–36) sessions, with stimulation intensity at 100% (96%–100%) threshold intensity, and the sham group received 33 (29–35) sessions.

Discussion

The findings of this international, multicentre, triple-blind, randomised sham-controlled trial show that, compared to 12 weeks of locomotor training alone, 12 weeks of locomotor training combined with tSCS

resulted in no additional improvement in walking ability. Our predefined minimally worthwhile treatment effect of 2 points on the WISCI-II lies well outside the 95% CI for our primary outcome (–1.6 to 1.5). There were also no additional improvements for the other secondary outcomes. It is important to note that, within the stimulation group, results did not differ regardless of whether stimulation was on or off. All outcome measures were assessed with the participants' allocated stimulation (real or sham) or without stimulation. This unique aspect of our study highlights that tSCS is ineffective as a rehabilitation tool and as a prosthetic device. In both groups, walking ability improved over time. The findings provide the first results from a fully-powered RCT of the combined effects of tSCS and locomotor training on walking ability in people with chronic SCI and limited walking ability.

We deliberately used a narrow inclusion criterion to select a relatively homogeneous group with limited walking ability (WISCI-II levels 1–6). Thus, our findings cannot be generalised to individuals with no walking ability (WISCI-II 0) or higher levels of walking ability (WISCI-II levels 7–20). Although the WISCI-II can be subjective and its levels do not necessarily reflect proportional increases in walking ability, assessors were blinded and, in most cases, were the same at each of the three assessment days for a given participant. Despite some limitations, the WISCI-II is reliable. The precision of our estimate confirms this.

Guess	Total count	Group allocation–stimulation	Group allocation–sham
Participants			
Reported stimulation	20	9	11
Reported sham	9	3	6
Did not know	19	12	7
Assessor			
Reported stimulation	14	9	5
Reported sham	5	3	2
Did not know	29	12	17

Therapists' reports are not included because multiple therapists were assigned to each participant.

Table 3: Participant and assessor reports of group allocation.

Additionally, we chose not to use objective measures such as the 10-m walk test or 6-min walk test due to intentionally including a cohort with limited mobility, as many participants would be unable to walk 10 m or sustain walking for 6 min.

Our results contrast with those of previous clinical studies and case series that report improved walking with tSCS.^{35–39} In response to the lack of RCT evidence, Comino-Suárez et al.¹⁶ conducted a randomised, sham-controlled clinical trial. Unfortunately, no power-calculation was performed for the primary outcome, making it unclear whether it was adequately powered. After 40 gait-training sessions (20 with tSCS) there was a between-group difference in walking (3.4 levels: 95% CI 0.5–6.4) on the WISCI-II with a modest increase in LEMS, measured one-month after the stimulation had stopped. The reason for this unexpected result is unclear but Comino-Suárez et al. studied participants with subacute SCI (1–5 months post injury) with a wide range of walking ability (12 [44%] had no function and 13 [48%] could walk 10 m).

The strength of our trial is its robust design, which used randomisation, triple blinding, and a sham control. In addition, it was powered to detect a meaningful difference in walking, the primary outcome measure. Our blinding and sham procedures were effective, ensuring that participants and assessors remained unaware of group allocation. The sham group was only exposed to 30–90s of real stimulation at 50% of threshold each session, a small dose that allowed clear comparison between locomotor training with tSCS and locomotor training alone.

Another strength of our trial was the rigorous monitoring and documentation of AEs and SAEs, an aspect often overlooked in stimulation studies. By systematically assessing blood pressure and skin integrity throughout training sessions, we collected extensive safety data related to autonomic dysreflexia (AD) and skin complications. Although the trial was not powered to evaluate safety as a primary outcome, several important findings emerged. There were five episodes of AD—one in the stimulation group and four in the sham group (this was the same individual). A 1 in 25 chance of triggering AD highlights the need for clinicians and participants to be fully informed of this risk, given its life-threatening nature. Another notable AE was a burn under the electrode site that progressed to a blister in one participant, emphasising the importance of monitoring and communicating the risk of skin injury.

Both groups of participants with chronic SCI in our study showed a similar improvement in walking ability at 12 and 16 weeks (~2.5 WISCI-II levels at 12 weeks). This change was seen both with and without stimulation. However, there was minimal change in LEMS and spasticity, regardless of group. This suggests that the improved walking with locomotor training likely

reflects improved gait strategies and muscle conditioning. Although our study and that of Comino-Suárez¹⁶ documented improved walking ability (after 36 and 20 training sessions respectively), some caution is required, as neither study enrolled a control group which did not have locomotor training.

Our study has some limitations. Several factors may have contributed to the lack of a treatment effect in the present study. First, our training dosage and period may have been insufficient. Participants in one tSCS pilot study completed 120 sessions (three sessions per week) and improvements were seen after >60 tSCS sessions.⁴⁰ However, without a sham control, it is impossible to know whether these gains were caused by tSCS combined with locomotor training or training alone (as in the present study). We chose a 12-week period with training sessions three times a week as an acceptable time commitment guided by feedback from the SCI community. Second, we did not include a pre-training period of locomotor training alone, as in some studies.¹⁶ Third, stimulation parameters, location, and intensity influence the effectiveness of tSCS to activate afferent and efferent nerve fibres. We chose a 10 kHz burst-modulated waveform over a conventional waveform because, at the time of trial design, it was claimed to evoke motor responses with less discomfort.⁴¹ However, this is now known to be incorrect⁴² and both waveforms are similarly effective at eliciting sEMR.⁴³ Although different muscles are preferentially recruited with different cathode placement,¹⁷ we confirmed similar sEMR thresholds across four lower limb muscle groups with the cathode placement used in this trial.¹⁷ In addition, there is no consensus about the optimal stimulation intensity.¹³ Some studies, like ours, standardise stimulus intensity relative to sEMR threshold,⁴⁴ but others stimulate above or below this intensity.³⁶ Other studies stimulate at the lowest intensity that evokes a visible contraction,⁷ limb movement,⁵ or paraesthesia³⁵ or at the highest intensity tolerated,¹⁶ which in people with SCI is often above or below the sEMR threshold. A complication with tSCS is that stimulation likely activates motor fibres directly as well as afferent fibres,⁴⁵ so that the changes in the lumbosacral cord are difficult to predict and vary between individuals.⁴⁶

In conclusion, the findings of this work show that 12-weeks of locomotor training with tSCS does not improve walking in people with chronic SCI with limited walking ability more than locomotor training alone.

Contributors

SG, JB, EB, CB, JD, ZD, MH, PH, BL, EM conceptualised the study. All authors were involved in data acquisition, analysis, or interpretation of data. EB wrote the first draft with input from CB, JB, SG. Statistical analysis was provided by JD and PH. SG, JB obtained funding. All authors have reviewed and agreed to the final version of the manuscript. EB, SG, JB, CB, ZD, MH, PH, JD accessed and verified the underlying data.

Data sharing statement

The project folder is available on the Open Science Foundation (OSF) at <http://osf.io/9s4wv/>. All de-identified participant data, statistical analysis code and the protocol can be found at <http://osf.io/9s4wv/files/stoage>.

Declaration of interests

EM has received funding from Wings for Life and Stoke Mandeville Spinal Research fund to investigate the use of spinal stimulation on walking and upper limb function. EM is a paid consultant to Liberate Medical LLC, KY, USA, which is developing an electrical stimulation device. MP has received funding from Research Fund, Stoke Mandeville Spinal Research Fund and the Inspire Foundation to investigate the use of spinal stimulation to improve upper limb function in acute and chronic tetraplegia and pain. MP has also been an invited member of the Scientific Committee for Spinal Research and Stoke Mandeville Spinal Research. JB has had paid airfares to give a plenary talk at Congress by the International Society for Electromyography and Kinesiology. All other authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.eclinm.2026.103802>.

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