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REVIEW

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Non-invasive cerebral and spinal cord stimulation for motor and gait recovery in incomplete spinal cord injury: systematic review and meta-analysis

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Abstract

Background Spinal cord injury (SCI) leads to gait impairment and loss of motor function and can be traumatic or non-traumatic in nature. Recently there has been important progress in the field of non-invasive central nervous stimulation, which can target the brain or spinal cord. In this review we aim to compare the effect of non-invasive cerebral and spinal cord stimulation on gait recovery and motor strength of lower limbs in subjects with SCI.

Methods We conducted a search (from September 2022 until March 2024) using the PubMed, Cochrane, and PEDro databases, including all studies published since the year 2000. The protocol of the review followed PRISMA guidelines and only RCTs scoring above 5 on the PEDro scale were selected.

Results A total of 12 RCTs with 341 participants were included. When all studies were pooled together, non-invasive central nervous system stimulation had significant effects on Lower Extremity Motor Scale (LEMS) score and gait speed. However, data was less apparent when subgrouped by type and level of stimulation. Repetitive transcranial magnetic stimulation (rTMS) showed large effect on LEMS, however transcranial direct current stimulation (tDCS) displayed a small effect on motor strength and gait speed. No meta-analysis could be performed for non-invasive spinal cord stimulation due to a lack of studies.

Conclusions When all non-invasive stimulation techniques were pooled together, significant effects on motor strength and gait function were observed. However, subgroup analyses based on stimulation types and levels revealed a significant reduction in these effects, particularly when categorized by stimulation type (rTMS and tDCS). Furthermore, a meta-analysis could not be conducted for non-invasive spinal cord stimulation due to a lack of studies (only one study each on tsDCS and tSCS). Therefore, more randomized controlled trials are needed to evaluate neuromodulation interventions in spinal cord injury, particularly at the spinal cord level.

Registration This systematic review with meta-analysis was registered in PROSPERO under the ID 512864.

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Background

Spinal cord injury (SCI) occurs when central nervous pathways are damaged, either through traumatic or non-traumatic events. These injuries affect motor, sensory and autonomic functions [1] and can result in significant physical disabilities, including loss of motor function below the level of injury.

Gait impairment is a prominent consequence of SCI, profoundly affecting mobility, independence, and quality of life, with walking recovery often highlighted as a primary goal of rehabilitation for individuals with SCI [2]. Thus, interventions and treatments aimed at improving motor function and mobility following such injuries carry a high-level of significance [2]. Various rehabilitation strategies, physical therapy techniques, assistive devices, and technological advancements are continuously being explored and developed to enhance the chances of walking recovery and improve overall quality of life for individuals affected by SCI [3, 4].

Walking is a complex process shaped by intricate neurological structures and feedback loops. Central motor programs in the brain collaborate with spinal feedback mechanisms to determine ambulatory capabilities. Key players in gait control are: (1) Motor and sensory cortex, managing voluntary movements and sensory information; (2) Basal ganglia, coordinating motor functions and movement modulation; (3) Brainstem, key for fundamental life processes and movement coordination; (4) Spinal cord: carry ascending and descending signals to and from higher cortical centres to lower motor neurones and contains central pattern generators (CPGs) which are crucial for rhythmic muscle activity during locomotion, activated by limb feedback. These four core elements interconnect, forming the foundation for our ability to walk, integrating brain commands with spinal cord and bodily responses [5].

Current research in gait rehabilitation primarily focuses on conventional therapies such as strength and fitness training, electrical muscle stimulation, and motor training [4, 6]. Additionally, other treatment modalities, including bodyweight supported treadmill training (BWSTT) [7], robot-assisted gait training (RAGT) [8, 9], spasticity management [10], and motor training [11] aimed at recovering functional capacities, have been utilized to promote further recovery [3, 12].

Non-invasive cerebral and spinal cord stimulation techniques (NIBS and NISCS respectively) represent a breakthrough frontier in medical science and offer promising avenues to improve motor and gait function in neurological disorders [13–17]. These innovative approaches leverage the power of technology to modulate neural activity without the need for invasive procedures, thereby reducing risks and improving patient outcomes [13, 14, 16, 17]. More specifically, recent research has increasingly investigated the effects of non-invasive stimulation on both the brain and spinal cord as part of the rehabilitation process. This includes NIBS as well as NISCS. One of the most researched NIBS methods is repetitive transcranial magnetic stimulation (rTMS). rTMS involves delivering magnetic pulses to specific areas of the brain, thereby affecting neuronal activity [18–20]. Another NIBS technique is transcranial direct current stimulation (tDCS), which consists of low electrical current applied through electrodes placed on the scalp that modulate neuronal excitability by facilitating or inhibiting synaptic transmission in targeted brain regions [21–23].

Transcutaneous spinal cord direct current stimulation (tsDCS) uses a weak direct current via skin surface electrodes. The use of tsDCS can modulate the spinal somatosensory pathways [24] and stimulate both ascending and descending pathways at spinal cord and cortical levels [24–28]. Transcutaneous spinal cord stimulation (tSCS) involves transcutaneous delivery of electrical impulses to the spinal cord via superficial electrodes and represents a parallel advance in non-invasive neuromodulation, particularly for the management of motor strength and gait function in neurological diseases [15, 16, 29]. The main difference between tSCS and tsDCS is that tSCS provides rests within the wave type, whereas in tsDCS the current is direct and provides no rest in its application [30]. In tsDCS, a low continuous intensity (1–2 mA) of current is typically used which is not modified between individual subjects. In contrast, tSCS can deliver a larger range of intensities from 5 up to 200 mA [16, 31–33]. Intensity threshold varies greatly from sensory to motor responses depending on each study. Also, depending on the type of stimulator used, some studies can deliver the intensity under a carrier frequency (between 5–10 kHZ), which is thought to maximise its penetration and improve the tolerance of stimulation.

In the present study, we conducted a systematic review with meta-analysis to demonstrate the effects of NIBS and NISCS, and to verify its effectiveness on gait and lower limb motor function recovery in subjects with SCI.

We hypothesized that non-invasive cerebral and spinal stimulation levels would be more effective than sham stimulation or control group in improving lower limb motor function related to gait function in persons with lower limb paralysis.

Methods

Registration

The protocol of this systematic review and meta-analysis follows the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [34]. The study was previously registered at The International Prospective Register of Systematic Reviews; PROSPERO (ID: 512864).

Search strategy

Relevant titles and abstracts were searched in Pubmed, Cochrane and the Physiotherapy Evidence Database (PEDro). Different searches were conducted by two team members (AHN, MW) up until March 2024.

Mesh terms Transcranial Magnetic Stimulation, Magnetic Field Therapy, Electric Stimulation Therapy, Transcranial Magnetic Stimulation, Spinal Cord Injuries, Gait were used. Other main major keywords were transcutaneous electric stimulation, transcutaneous spinal cord direct current stimulation, transcutaneous spinal cord stimulation, non-invasive stimulation. Results were also filtered with Boolean operator NOT for FES (Functional Electrical Stimulation). Only records of randomized control trials (RCT) from the year 2000 onwards were selected. After removal of duplicate articles, results were screened by their title and abstracts. The final selection was categorized according to NIBS or NISCS interventions.

Eligibility criteria

The inclusion criteria followed the PRISMA checklist:

Participants: individuals with traumatic and non-traumatic motor incomplete SCI; *Interventions*: non-invasive brain stimulation, non-invasive spinal cord stimulation, transcranial magnetic stimulation (rTMS), transcranial direct current stimulation (tDCS), transcutaneous spinal cord direct current stimulation (tsDCS), transcutaneous spinal cord stimulation (tSCS); *Comparators*: sham or control group; *Outcomes*: Lower Extremity Motor Scale (LEMS), 10 m walking test (10MWT) (velocity, cadence, stride), 6 min walking test (6MWT), Timed Up and Go Test (TUG), Walking Index for Spinal Cord Injury (WISCI); study design: randomized controlled clinical trial (RCT); languages: English or Spanish. Articles were excluded if the study was not an RCT, if there was insufficient or inconsistent data (even when contacting the authors), or if they scored less than 5 in the PEDro scale.

Data collection

Three researchers (AHN, ARA, and MY) extracted the data from the included studies. Three sets of data were collected.

Firstly, main data about studies was collected: stimulation modality, number of participants (and distribution into intervention and control groups), age (range, mean and standard deviation), SCI level, AIS classification, time since injury (mean and standard deviation), concurrent therapies and outcome measures. Secondly, technical characteristics of interventions: stimulation modality, stimulation area, number of sessions, stimulation protocol and device. Finally, data of selected outcomes was extracted. This included initial, final and follow-up means and standard deviation for motor and gait outcome measures (LEMS, 10MWT, 6MWT, TUG, WISCI). Article authors were contacted to further complete the missing data and information was received for two studies [35, 36].

We performed a meta-analysis using two methods of grouping data: (1) pooled data from all studies (non-invasive cerebral and spinal cord stimulation), (2) analysis of each type and level of stimulation separately (rTMS, tDCS, tsDCS, tSCS).

Methodological quality assessment and statistical analysis

The Physiotherapy Evidence Database (PEDro) scale was applied to evaluate the methodological quality of the studies by two researchers (AHN and MW) who measured it independently for each study. Differences in opinion were discussed and, if needed, resolved with a third party. Table 1 shows the results of the methodological quality assessment. The interpretation of PEDro scale scores is as follows: 9–11 "excellent quality," 6–8 "good quality," 4–5 "fair quality," 3 or lower "poor quality." The set of articles averaged 8 on the PEDro scale. All studies specified eligibility criteria, conducted random allocation, and blinded the subjects.

Standard meta-analytic methods were conducted to estimate an overall comparative effect size between intervention and non-intervention groups by Microsoft Excel and Jasp (University of Amsterdam) for LEMS, velocity m/s (10MWT), steps/min (10MWT), WISCI and TUG. Main collected and synthesized data were mean ± standard deviation (Mean ± SD) of initial, final and follow-up records. Effect size was calculated using the Cohen's d definition (0.10 small; 0.30 medium; 0.50 large effect).

Results

Study identification

The search retrieved a total of 400 records. After 217 duplicated entries were removed, 183 studies were

Table 1 Methodological assessment of selected articles

	Eligibility criteria specified	Random allocation	Concealed allocation	Comparable baseline	Subject blinding	Therapist blinding	Assessor blinding	Less than 15% dropouts	Intention-to-treat analysis	Between group comparison	Point estimates and variability	Total score
Benito, 2012 [37]	1	1	0	1	1	0	1	1	1	1	1	**8**
Kumru, 2016 [38]	1	1	0	1	1	0	1	1	1	1	1	**8**
Krogh, 2022 [39]	1	1	1	1	1	0	0	1	1	1	1	**8**
Kesikburun, 2023 [40]	1	1	1	1	1	0	1	1	1	1	1	**9**
Raithatha, 2016 [41]	1	1	0	1	1	1	1	1	1	1	1	**9**
Kumru, 2016 [42]	1	1	0	1	1	0	1	1	1	1	1	**8**
Simis, 2021 [43]	1	1	1	1	1	0	1	1	1	1	1	**9**
Evans, 2022 [44]	1	1	1	0	1	1	1	1	1	1	1	**9**
Klamruen, 2023 [36]	1	1	1	1	1	0	1	1	1	1	1	**9**
Nijhawan, 2024 [45]	1	1	1	1	1	0	1	1	0	1	1	**8**
Lin, 2023 [46]	1	1	0	0	1	0	1	1	1	1	1	**7**
Estes, 2021 [47]	1	1	0	1	0	0	0	1	0	1	1	**5**

The bold format in total score column highlights the overall outcome for PEDro scale

screened by their title and abstract, leading to 146 studies being excluded. During the process, 11 more registries were included by manual search and bibliography referencing. A final sum of 49 studies were full text screened for eligibility. 37 articles were excluded, and the final selection consisted of 12 articles, 11 for NIBS and 2 for NISCS (Fig. 1 Flowchart).

Study selection and stimulation characteristics

Main characteristics of the studies can be found in Table 2. Characteristics of stimulation types and protocols are shown in Table 3. All the included studies were parallel RCTs. The NIBS category was comprised of 11 articles, 5 applied rTMS [37–40, 46], and 6 applied tDCS [36, 41–45]. The NISCS category included 2 articles, one applied transcutaneous spinal direct current stimulation (tsDCS) [46] and the other tSCS [47].

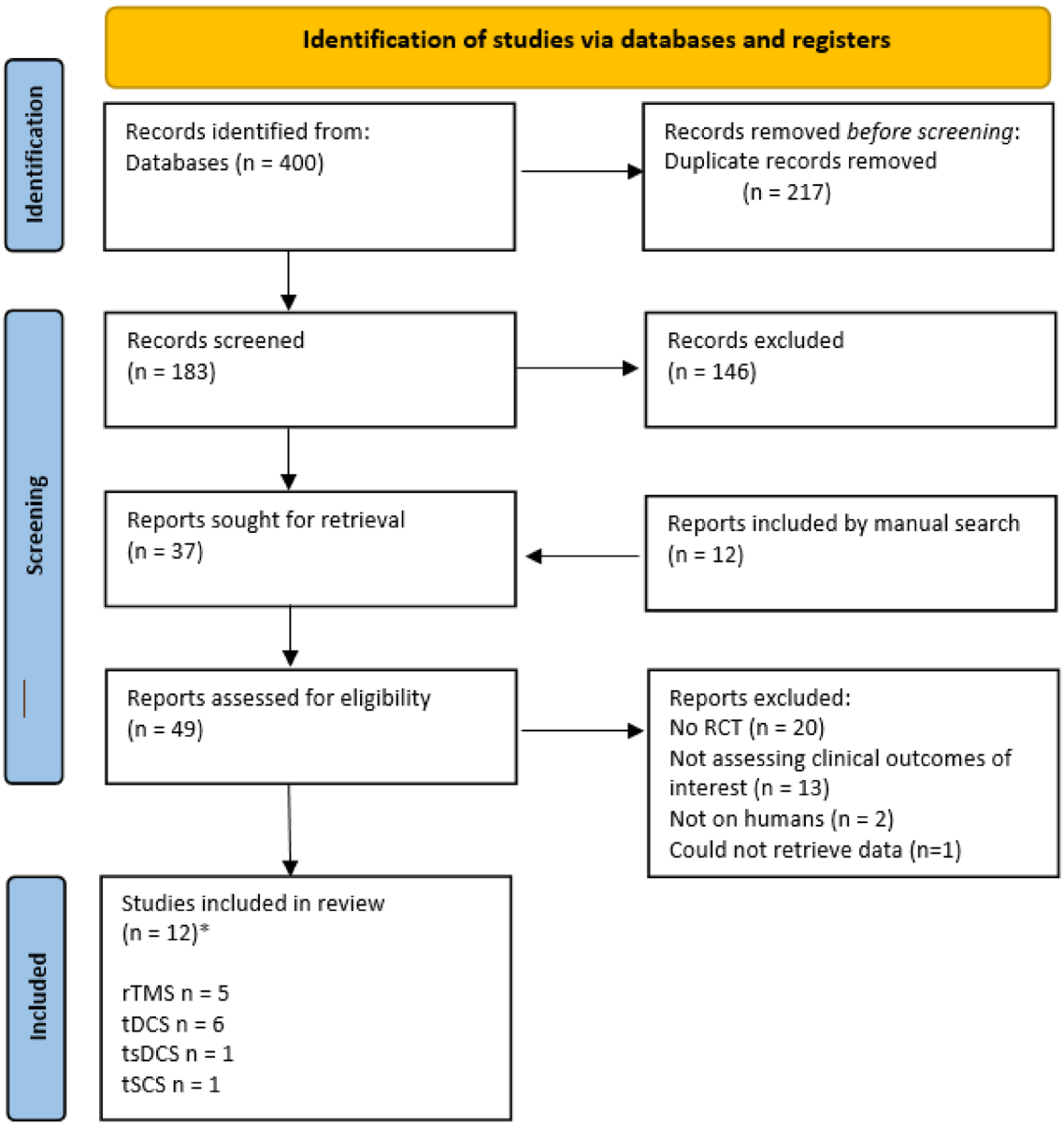


Fig. 1 PRISMA diagram flowchart for study selection. *Note*: * One study [46] included experiments on both techniques at the same time. n: number of studies; RCT: randomized controlled trial; rTMS: repetitive trancranial magnetic stimulation; tDCS: transcranial direct current stimulation; tsDCS: transcutaneous spinal direct current stimulation; tSCS: transcutaneous spinal cord stimulation.

Table 2 Main studies characteristics

	Stimulation modality	Intervention group vs control group	Age (years)			SCI level	AIS	Time since injury		Concurrent therapy	Control group intervention	Outcome measures
			Range	Mean	SD			Mean	SD			
Benito, 2012 [37]	rTMS	10/10 †	18–60	33.5	14.41	C4 T12	D	8 months	3.19	5 h daily of ADL, PT, OT, sport, HT, GT	Concurrent therapy + sham stimulation	LEMS, MAS, 10MWT, WISCI II, TUG
Kumru, 2016 [38]	rTMS	17/17	19–69	51	15.61	C3-T12	C, D	2.5 months	1.45	5 h daily of ADL, PT, OT, sport, HT, GT		LEMS, WISCI II, 10MWT
Krogh, 2022 [39]	rTMS	11/9	35–70	57	10.37	C2 L2	A, C, D	81 days	54.65	RT, PT, HT, OT, ADL, EBE*		LEMS, 10MWT, TUG, 6MWT
Kesikburun, 2023 [40]	rTMS	14/14	18–45	35.7	12.1	NA	C, D	28.8 months 34.5 months	15.3 27.5	GT, ST, BT		LEMS, WISCI II, 10MWT
Raithatha, 2016 [41]	tDCS	9/6	24–67	54	12.26	C4 L1	B, C, D	2 years	11.17	RAGT		6MWT, 10MWT, TUG
Kumru, 2016 [42]	tDCS	12/12	21–71	54.5	14.27	C1-T12	C, D	3 months	1.98	5 h daily of ADL, PT, OT, sport, HT, GT		LEMS, WISCI II, 10MWT
Simis, 2021 [43]	tDCS	21/22	28–45	38	NA	NA	C, D	16 months	NA	RAGT		WISCI-II, 10MWT, 6MWT, TUG
Evans, 2022 [44]	tDCS	11/14	19–69	50.0	13.16	C4 T8	C, D	46 months	87.18	MST		10MWT, cadence, stride length
Klamruen, 2023** [36]	tDCS	17/17	NA	41.8 48.4	13.5 13.36	NA	C, D	17 months 12 months	NA	GT		10MWT, TUG
Nijhawan, 2024** [45]	tDCS	17/18	NA	30 28.38	10.6 10.12	NA	B, C, D	21.88 months 71.88 months	20.24 16.94	None	Sham stimulation	LEMS
Lin, 2023 [46]	tsDCS/ rTMS/ tsDCS + rTMS	3/3/3	42–65	58.1	7.2	C5 T6	C, D	5.2 years	3.02	30 min cycling		LEMS
Estes, 2021 [47]	tSCS	8/8	18–65	51.5	15.7	C2 T11	B, D	83.5 days	46.4	GT/RAGT	Concurrent therapy + sham stimulation	10MWT, 2mWT

C cervical, *T* thoracic, *L* lumbar, *SD* standard deviation, *NIBS* non-invasive brain stimulation, *NISCS* non-invasive spinal cord stimulation, *rTMS* repetitive Transcranial Magnetic Stimulation, *tDCS* transcranial Direct Current Stimulation, *tSCS* transcutaneous Spinal Cord Stimulation, *tsDCS* transcutaneous spinal direct current stimulation, *ADL* activities of daily life, *PT* physical therapy, *OT*, occupational therapy, *HT* hydrotherapy, *GT* gait training, *RT* resistance training, *EBE* evidence based exercise, *MST* motor skill training, *ST* strength training, *BT* balance training, *RAGT* robot-assisted gait training, *LEMS* Lower Extremity Motor Scale, *MAS* Modified Ashworth Scale, *10MWT* 10 m walk test, *WISCI II* Walking Index Spinal Cord Injury, *TUG* Timed Up and Go test, *2mWT* 2 m walking test, *6MWT* 6 min walking test, *NA* not available

*SCI Action International's guidelines

**For these studies, TSI and age are shown as group segregated (intervention group first and control group secondly)

† A total of 17 subjects were recruited with initial distribution of intervention group 7 and control group 10. Later, 3 subjects crossed over to active rTMS group after finishing the protocol. Results did not differ to original rTMS group. Data from this article are shown based on intervention group 10 and control group 10 distribution.

Table 3 Stimulation parameters and sessions

	Stimulation modality	Stimulation area	Number of sessions	Stimulation protocol	Device	Gait training
rTMS						
Benito, 2012 [37]	rTMS	Vertex	15 Sessions Before training 5 days/week × 3 weeks	20 Hz × 40 pulses/burst × 90% RMT Intervals of 28 s Total: 1800 pulses over 20 min	MagStim Super Rapid magnetic stimulator (Magstim Company, UK) with double cone coil	Concurrent therapy
Kumru, 2016 [38]	rTMS	Vertex	20 Sessions Before training 5 days/week × 4 weeks	20 Hz × 40 pulses/burst × 90% RMT Total: 1800 pulses over 20 min	Magstim Super Rapid magnetic stimulator (Magstim Company Ltd., UK) with double-cone coil	Lokomat® training 30 min/session
Krogh, 2022 [39]	rTMS	Vertex	20 Sessions Before training 5 days/week × 4 weeks	20 Hz × 45 trains with 28 s rest in-between 40 pulses × 100% RMT Total: 1800 pulses over ~ 22 min	Magstim Super Rapid2 Plus stimulator (The Magstim Company Ltd., UK) with double-cone coil (The Magstim Company Ltd, UK)	Concurrent therapy
Kesikburun, 2023 [40]	rTMS	Vertex	15 Sessions Before training 5 days/week × 3 weeks	20 Hz × 40 trains × 2 s Inter-train interval of 28 s Total 1.600 pulses	Magstim Rapid2 Magnetic Stimulator (Magstim, UK) with 8-shaped coil with an outer loop diameter of 70 mm (Air Film Coil, Magstim, UK)	30 min gait training
Lin, 2023 [46]	iTBS rTMS	Vertex	24 Sessions Before training 3 days/week × 8 weeks	5 Hz × 10 bursts, intensity: 90% RMT, total 600 stimulations	MagPro R30, (MagVenture, Denmark) with a Cool-B65 coil	Concurrent therapy
tDCS						
Raithatha, 2016 [41]	tDCS	*Anode*: cortical LE motor area *Cathode*: 35 cm^2 supraorbitally	36 Sessions During training 3 days/ week × 12 weeks	Intensity: 2 mA Current density of 0.08 mA/cm^2 Charge density: 960 Coulombs/M2 Time: 20 min	Not specified	Lokomat® training
Kumru, 2016 [42]	tDCS	*Anode*: leg motor cortex (vertex) *Cathode*: non-dominant supraorbital area	20 Sessions During training 5 days/week × 4 weeks	Intensity: 2 mA Time: 20 min	Battery driven constant current stimulator (NeuroConn-GmbH, Germany) with saline-soaked sponge electrodes [30 cm^2]	Lokomat® training 30 min
Simis, 2021 [43]	tDCS	*Anode*: Cz *Cathode*: over contralateral supraorbital region	30 Sessions Before training 3 sessions/week × 10 weeks	Continuous current 2 mA Current ramp up and onset of 30 s each Time: 20 min	Monophasic current device (DC stimulator, NeuroCom, Germany or Soterix Medical, New York, EUA) and sponge surface electrodes [35 cm^2] soaked in saline solution	Lokomat® training 30 min

Table 3 (continued)

	Stimulation modality	Stimulation area	Number of sessions	Stimulation protocol	Device	Gait training
Evans, 2022 [44]	tDCS	*Anode* : slightly anterior to vertex *Cathode* : inion	3 Sessions in 5 days During concurrent therapy	Calculated current density: 0.80 A/m2 Charge density: 0.96 kC/m^2	ActivaDose II, (Activa Tek Inc, California) with two 5 × 5 cm 0.9% saline-soaked electrodes	Concurrent therapy
Klamruen, 2023 [36]	tDCS	*Anode* : vertex *Cathode* : right supraorbital region	5 Sessions (1 per day) Before training	2.0 mA Ramp up and ramp down period of 30 s Time. 20 min	Ybrain (MINDDSTIM) with rectangular saline-soaked sponge pad electrode measuring 35cm^2 (5 × 7 cm)	Overground gait training 40 min
Nijhawan, 2024 [45]	tDCS	*Anode*: C3/C4 opposite to affected lower limb *Cathode* : opposite supraorbital area	10 Sessions Before rehabilitation 5 days/week × 2 weeks	2 mA Time: 20 min	With two saline-soaked sponge electrodes (1.5 inches diameter)	Standard rehabilitation
tsDCS						
Lin, 2023 [46]	tsDCS	*Anode*: T11-T12 *Cathode*: left shoulder	24 Sessions Before training 3 days/week × 8 weeks	2.5 mA	Electrical Stimulator and Control Device	Concurrent therapy
tSCS						
Estes, 2021 [47]	tSCS	*Anode*: over vertebral levels T11/T12 *Cathode*: over the umbilicus	6 Sessions During Lokomat® training 3 days/ week × 2 weeks	39–100 mA, 50 Hz, biphasic pulses Time: 30 min Tingling sensation, highest tolerance level. Subthreshold for lower extremity muscle activation	Portable electrotherapy device (Empi Continuum, USA) and stimulating electrode (5 cm round electrode)	Lokomat® training 60 min/session after stimulation (including setup and take down)

L intermittent Theta Burst Stimulation, *NIBS* non-invasive brain stimulation, *NISCS* non-invasive spinal cord stimulation, *T* repetitive Transcranial Magnetic Stimulation, *tSCS* transcutaneous Spinal Cord Stimulation, *tDCS* transcranial Direct Current Stimulation, *tvDCS* transvertebral Direct Current Stimulation, *RMT* resting motor threshold, *MST* motor skill training, *LT* locomotor training

Subject sample sizes and study designs

Overall, all RCTs included a total number of 341 participants. Mean age of participants in the studies was 48.3 years, with a range between 18 and 70 years old (Table 2). Most injury levels were comprised between C1 and T12, with two studies including lesions caudally until L1-L2 [39, 41]. Main AIS classifications were B and D, but one study included subjects with AIS A lesions [39]. Almost all studies included concurrent therapies, mainly based on evidenced based exercise, gait training, strength training or motor skill training (Table 2).

Effects of interventions

Statistics were performed for all studies, as well as sorted by group, depending on the type of treatment. Consequently, available data allowed the analysis of two groups: rTMS and tDCS. For non-invasive spinal cord stimulation (tsDCS and tSCS) category there were not enough studies to perform statistical meta-analysis.

Meta-analysis of NIBS and NISCS pooled together

There were seven RCT studies with non-invasive brain stimulation which included LEMS score: 5 applied rTMS [37–40, 46] while 2 applied tDCS [42, 45], and 1 applied rTMS and tsDCS [46]. The study of Lin et al. [46] is presented in Table 4 with two different groups in the graphs to represent the different conditions of groups depending on the used technique. There was only one study that applied non-invasive spinal stimulation and included LEMS evaluation [46]. When all groups were included, data showed an overall large effect (0.697) for between group effect size comparison.

Five studies carried out LEMS follow-up evaluation, with an overall medium effect (0.36) [38, 40, 42, 45, 46].

Velocity (m/s) in the 10MWT pre and post intervention was analysed in 5 studies [36, 37, 40, 44, 47]. Overall effect size was small (0.19). Two studies used rTMS [37, 40], 2 applied tDCS [36, 44], and 1 tSCS [47].

The Timed Up and Go test (TUG) was assessed in 2 studies [36, 37] with a medium effect size (0.42). One study used tDCS [36] and 1 applied rTMS [37].

The Walking Index for Spinal Cord Injury (WISCI) was reported in 3 studies [36, 37, 43] with a large effect size (0.63). Two applied tDCS [36, 43] and 1 used rTMS [37].

rTMS

Stimulation at a high frequency (20 Hz), over 90% of the resting motor threshold (RMT) with more than 1600 pulses were delivered in all rTMS studies, except for Lin et al. 2023 [46] that delivered 600 pulses at 5 Hz frequency. The RMT reflects the excitability of corticomotor projections during muscle relaxation and is used to individually adjust the intensity of TMS. Number of sessions was similar (between 15 and 24), and the stimulation area was the vertex in all studies (Table 3).

LEMS was assessed in all 5 studies [37, 39, 40, 42, 46] (Table 5). The overall effect size was large (1.050). Of these 5 studies, only 3 sets of data for LEMS follow-up evaluation score were available [38, 40, 46] with a medium effect size (0.442). The follow-up evaluation differed from the three studies being 4, 5 and 4 weeks [38, 40, 46].

Two studies used the 10MWT to report gait velocity (m/s) [37, 40] with a small effect size (0.149). WISCI was assessed in 2 studies [37, 40] with a small effect size (0.155).

tDCS

All tDCS studies performed stimulation at an intensity of 2 mA for 20 min. Placement of electrodes was similar between studies, with the anode over the vertex or motor cortex areas and the cathode on the opposite supraorbital area or union. Number of sessions differed greatly (from 3 to 36 sessions) (Table 3).

LEMS score was assessed in two tDCS studies [42, 45] (Table 6). Both data sets for pre vs. post and pre vs. follow-up presented small effect sizes (0.147 and 0.294 respectively). Velocity in 10MWT was assessed in 2 tDCS studies [36, 44] with a small effect size (0.17). The follow-up evaluations differed from 2 to 4 weeks.

tsDCS and tSCS

There were not enough articles to conduct a meta-analysis for NISCS. One study applied tsDCS in 3 participants, who received 3 sessions of 20 min per week for 2 months [46]. LEMS was assessed but did not show any significant improvement.

tSCS was only studied by Estes et al., being applied in 18 subjects with SCI across a 4-week program [47]. Gait analysis was assessed using the 10MWT and 2-min walking tests, along with spatiotemporal gait characteristics. The tSCS group showed a significant improvement in walking speed and a large effect size (0.43).

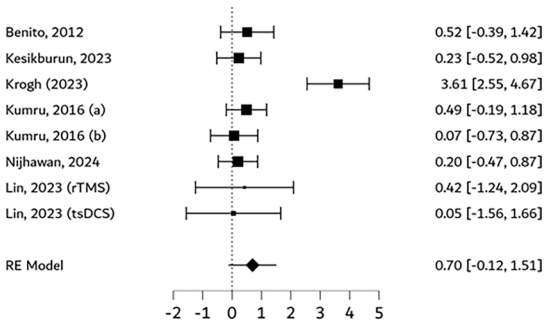
Discussion

When all non-invasive stimulation techniques, targeting either the cortical or spinal cord levels, were pooled together, significant effects on motor strength of lower limb (LEMS) and gait function were observed. However, this overall data became less apparent when subgroup analyses were conducted based on stimulation types and level such as rTMS, tDCS, tsDCS and tSCS. The effect sizes reduced significantly as expected, particularly when categorized by the type of stimulation (rTMS and tDCS)

Table 4 Non-invasive brain and spinal cord stimulation—all studies

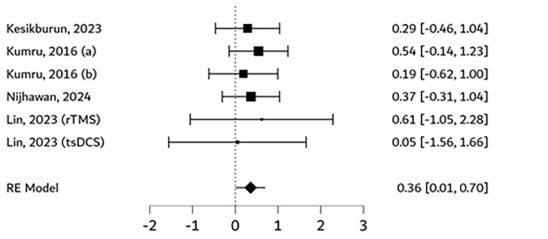
LEMS SCORE /50 initial-final

Article	Technique	Group	n	Initial Mean	Initial SD	Final Mean	Final SD	Effect size groups x time Cohen's d	SE
Benito, 2012 (37)	rTMS	Active	10	28.4	6.5	33.2	8.4	0.52	0.46
		Sham	10	29,6	4,8	30,9	7		
Kesikburun, 2023 (40)	rTMS	Active	14	32.6	8.9	35.4	8.7	0.23	0.38
		Sham	14	36	11	36.5	11.2		
Krogh, 2022 (39)	rTMS	Active	11	28	5.75	40.5	3.75	3.61	0.54
		Sham	9	42	4.75	39	2		
Kumru, 2016 (38)	rTMS	Active	17	23.1	10	31.4	10.3	0.49	0.35
		Sham	17	19.4	11	22.6	10.4		
Kumru, 2016 (42)	tDCS	Active	12	20.5	9.2	23.9	9	0.07	0.41
		Sham	12	18.7	10.3	22.8	11.4		
Nijhawan, 2024 (45)	tDCS	Active	17	23.69	11.5	26.88	12.99	0.20	0.34
		Sham	18	28	11.88	28.75	12.06		
Lin, 2023 (46)	rTMS	Active	3	36.5	8.5	38	6	0.42	0.85
		Sham	3	42.5	6.5	41	7		
	tsDCS	Active	3	34	12	33	13	0.05	0.82
		Sham	3	42.5	6.5	41	7		



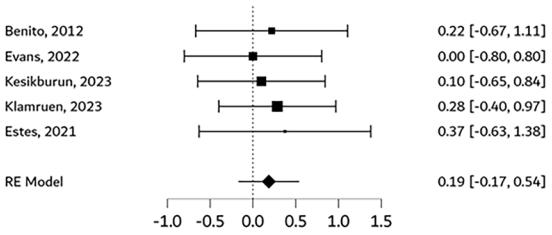
LEMS SCORE /50 initial-follow up

Article	Technique	Group	n	Initial Mean	Initial SD	Follow up Mean	Follow up SD	Effect size groups x time Cohen's d	SE
Kesikburun, 2023 (40)	rTMS	Active	14	32.6	8.9	36.2	8.8	0.29	0.38
		Sham	14	36	11	36.7	11.3		
Kumru, 2016 (38)	rTMS	Active	17	23.1	10	34.9	10.1	0.54	0.35
		Sham	17	19.4	11	25.4	11.8		
Kumru, 2016 (42)	tDCS	Active	12	20.5	9.2	27.3	4.4	0.19	0.41
		Sham	12	18.7	10.3	26.9	3.2		
Nijhawan, 2024 (45)	tDCS	Active	17	23.69	11.5	30	13.63	0.37	0.34
		Sham	18	28	11.88	29.87	11.5		
Lin, 2023 (46)	rTMS	Active	3	36.5	8.5	38.5	6.5	0.61	0.87
		Sham	3	42.5	6.5	40.5	3.5		
	tsDCS	Active	3	34	12	32.5	13.5	0.05	0.82
		Sham	3	42.5	6.5	40.5	3.5		



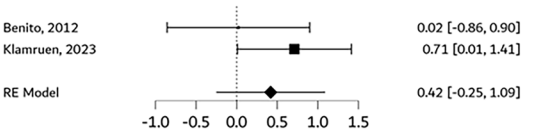
10MWT velocity initial final

Article	Design	Group	n	Initial Mean	Initial SD	Final Mean	Final SD	Effect size groups x time Cohen's d	SE
Benito, 2012 (37)	rTMS	Active	10	0.24	0.32	0.40	0.44	0.22	0.45
		Sham	10	0.26	0.20	0.35	0.27		
Evans, 2022 (44)	tDCS	Active	11	0.64	0.51	0.77	0.46	0.00	0.41
		Sham	13	0.72	0.53	0.85	0.56		
Kesikburun, 2023 (40)	rTMS	Active	14	0.41	0.28	0.49	0.28	0.10	0.38
		Sham	14	0.37	0.30	0.42	0.35		
Klamruen, 2023 (36)	tDCS	Active	17	0.52	0.32	0.73	0.44	0.29	0.35
		Sham	17	0,65	0,10	0,76	0,43		
Estes, 2021 (47)	tSCS	Active	8	0.66	0.38	0.82	0.28	0.37	0.51
		Sham	8	0.32	0.14	0.38	0.21		



TUG initial-final

Article	Design	Groups	n	Initial Mean	Initial SD	Final Mean	Final SD	Effect size group x time Cohen's d	SE
Benito, 2012 (37)	rTMS	Active	10	84.60	76.10	62.10	57.90	0.02	0.45
		Sham	10	74.00	55.80	52.80	39.20		
Klamruen, 2023 (36)	tDCS	Active	17	75.65	21.38	25.50	21.71	0.71	0.36
		Sham	17	81.65	18.86	17.25	18.00		

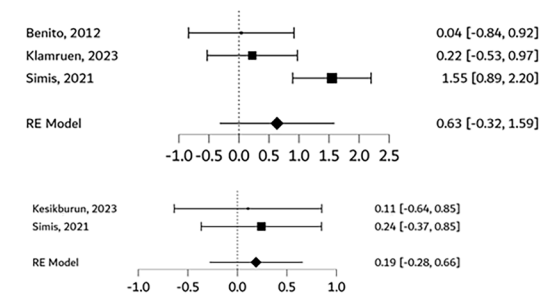


WISCI /20 initial-final

Article	Design	Group	n	Initial Mean	Initial SD	Final Mean	Final SD	Effect size group x time Cohen's d	SE
Benito, 2012 (37)	rTMS	Active	10	9.50	5.70	11.10	4.40	0.04	0.45
		Sham	10	10.30	5.60	12.10	4.60		
Kesikburun, 2023 (40)	rTMS	Active	14	14.80	3.20	15.60	3.40	0.22	0.38
		Sham	14	15.60	3.90	15.60	3.90		
Simis, 2021 (43)	tDCS	Active	21	9.90	7.40	23.10	6.30	1.55	0.33
		Sham	22	8.50	7.70	10.80	6.70		

WISCI /20 initial-follow up

Article	Design	Group	n	Initial Mean	Initial SD	Follow up Mean	Follow up SD	Effect size group x time Cohen's d	SE
Kesikburun, 2023 (40)	rTMS	Active	14	14.80	3.20	15.20	3.70	0.11	0.38
		Sham	14	15.60	3.90	15.60	3.90		
Simis, 2021 (43)	tDCS	Active	21	9.90	7.40	13.70	6.20	0.24	0.31
		Sham	22	8.50	7.70	10.60	6.70		



and no meta-analysis could be performed for non-invasive spinal cord stimulation due to a lack of studies (1 in tsDCS and 1 in tSCS).

When high frequency rTMS was applied over the leg motor cortex area at 5–20 Hz, between 15–24 sessions, it induced a long-lasting improvement in motor strength

Table 5 rTMS

LEMS SCORE initial-final

Article	Technique	Group	n	Initial Mean	Initial SD	Final Mean	Final SD	Effect size groups x time Cohen's d	Effect size groups x time SE
Benito, 2012 (37)	rTMS	Active	10	28.4	6.5	33.2	8.4	0.52	0.46
		Sham	10	29.6	4.8	30.9	7		
Kesikburun, 2023 (40)	rTMS	Active	14	32.6	8.9	35.4	8.7	0.23	0.38
		Sham	14	36	11	36.5	11.2		
Krogh, 2022 (39)	rTMS	Active	11	28	5.75	40.5	3.75	3.61	0.54
		Sham	9	42	4.75	39	2		
Kumru, 2016 (38)	rTMS	Active	17	23.1	10	31.4	10.3	0.49	0.35
		Sham	17	19.4	11	22.6	10.4		
Lin, 2023 (46)	rTMS	Active	3	36.5	8.5	38	6	0.42	0.85
		Sham	3	42.5	6.5	41	7		

LEMS SCORE initial-follow up

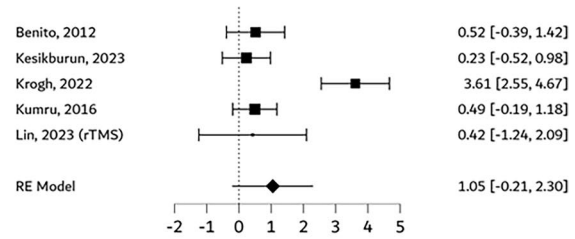
Article	Technique	Group	n	Initial Mean	Initial SD	Follow up Mean	Follow up SD	Effect size groups x time Cohen's d	Effect size groups x time SE
Kesikburun, 2023 (40)	rTMS	Active	14	32.6	8.9	36.2	8.8	0.29	0.38
		Sham	14	36	11	36.7	11.3		
Kumru, 2016 (38)	rTMS	Active	17	23.1	10	34.9	10.1	0.54	0.35
		Sham	17	19.4	11	25.4	11.8		
Lin, 2023 (46)	rTMS	Active	3	36.5	8.5	38.5	6.5	0.61	0.87
		Sham	3	42.5	6.5	40.5	3.5		

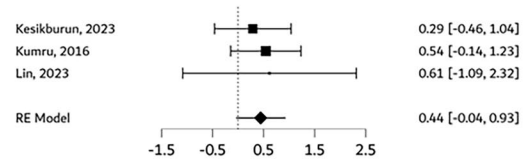
WISCI /20 initial-final

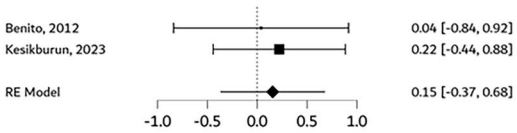
Article	Design	Group	n	Initial Mean	Initial SD	Final Mean	Final SD	Effect size group x time Cohen's d	Effect size group x time SE
Benito, 2012 (37)	rTMS	Active	10	9.50	5.70	11.10	4.40	0.04	0.45
		Sham	10	10.30	5.60	12.10	4.60		
Kesikburun. 2023 (40)	rTMS	Active	14	14.80	3.20	15.60	3.40	0.22	0.38
		Sham	14	15.60	3.90	15.60	3.90		

10MWT velocity initial-final

Article	Design	Group	n	Initial Mean	Initial SD	Final Mean	Final SD	Effect size groups x time Cohen's d	Effect size groups x time SE
Benito, 2012 (37)	rTMS	Active	10	0.24	0.32	0.40	0.44	0.22	0.45
		Sham	10	0.26	0.20	0.35	0.27		
Kesikburun, 2023 (40)	rTMS	Active	14	0.41	0.28	0.49	0.28	0.10	0.38
		Sham	14	0.37	0.30	0.42	0.35		







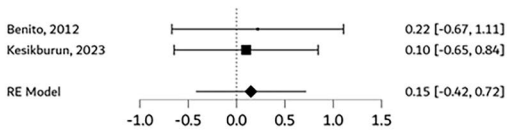


Table 6 tDCS

LEMS SCORE initial-final

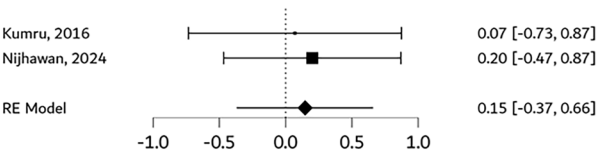
Article	Technique	Group	n	Initial Mean	Initial SD	Final Mean	Final SD	Effect size groups x time Cohen's d	Effect size groups x time SE
Kumru, 2016 (42)	tDCS	Active	12	20.5	9.2	23.9	9	0.07	0.41
		Sham	12	18.7	10.3	22.8	11.4		
Nijhawan, 2024 (45)	tDCS	Active	17	23.69	11.5	26.88	12.99	0.20	0.34
		Sham	18	28	11.88	28.75	12.06		

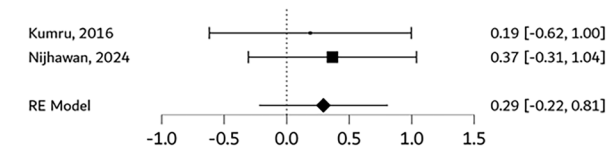
LEMS SCORE initial-follow up

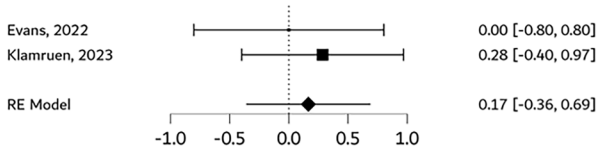
Article	Technique	Group	n	Initial Mean	Initial SD	Follow up Mean	Follow up SD	Effect size groups x time Cohen's d	Effect size groups x time SE
Kumru, 2016 (42)	tDCS	Active	12	20.5	9.2	27.3	4.4	0.19	0.41
		Sham	12	18.7	10.3	26.9	3.2		
Nijhawan, 2024 (45)	tDCS	Active	17	23.69	11.5	30	13.63	0.37	0.34
		Sham	18	28	11.88	29.87	11.5		

10MWT velocity initial-final

Article	Design	Group	n	Initial Mean	Initial SD	Final Mean	Final SD	Effect size groups x time Cohen's d	Effect size groups x time SE
Evans, 2022 (44)	tDCS	Active	11	0.64	0.51	0.77	0.46	0.00	0.41
		Sham	13	0.72	0.53	0.85	0.56		
Klamruen, 2023 (36)	tDCS	Active	17	0.52	0.32	0.73	0.44	0.28	0.35
		Sham	17	0.65	0.10	0.76	0.43		







of the lower limb. However, rTMS influence on gait function presented a small effect. Recent scientific literature has shown promising results in rTMS, enhancing neuroplasticity and promoting motor and gait improvements in individuals with SCI. When applied to the motor cortex, high frequency rTMS increased the excitability of the corticospinal tract, leading to prolonged beneficial effects that extended beyond the stimulation sessions [37, 38, 48–50]. The underlying mechanisms of these effects are not yet fully understood; however, it is hypothesized that rTMS may induce changes in synaptic efficacy, possibly related to long-term potentiation (LTP) [51]. LTP is

a process where synaptic connections are strengthened through repeated stimulation, which enhances signal transmission between neurons. This synaptic strengthening could contribute to the observed improvements in motor function and gait in SCI patients following rTMS treatment. In our results on rTMS, we found significant changes in motor scores in five studies, but only two of them showed improvements (small effects) in gait function. This discrepancy could be due to several factors: Firstly, most of the included studies assessing motor strength lacked specific gait evaluations, with only two of them assessing gait function. Furthermore, gait improvement depends on a rhythmic correlation of timed muscle activations, especially between stance and swing phases. Large proximal muscles tend to assist more during propulsion phases, while distal ankle muscles play a key role in balance and the stance phase [52–54]. The gains in specific muscle motor scores may not be directly correlated to gait because the observed motor improvements might not relate to specific gait phases. Also, in individuals with cervical SCI, the impairment of upper extremity and trunk muscles may significantly impact walking ability. Given that arm movements and upper body stability play a critical role in maintaining balance and coordination during gait, the loss of upper limb and trunk function in cervical SCI patients could further limit their capacity to walking [55–58]. While overall motor capacity may improve, these changes do not necessarily lead to measurable enhancements in gait performance. Factors contributing to this outcome may include the level of the neurological injury—whether cervical, thoracic, or lumbar—as well as the severity of the injury. For instance, one study included patients with AIS grade A [39]. Additionally, the relatively short time since the injury may also influence the results.

Small effects for lower limb motor strength and gait velocity were shown for tDCS conducted at 2–2.5 mA for 20 min across 10–36 sessions with the anode over the vertex or the C3/C4 brain area opposite to the affected lower limb. tDCS delivers a continuous current (1–2.5 mA) through the scalp of the subject, with the anode (positive red electrode) thought to excite (depolarize) the underlying neural structure. It does not modify the action potential directly, as the excitatory effects depend on the specific area where the tDCS predominantly acts, such as the somatodendritic compartment, interneurons, or long-axon endings [59, 60]. Stimulation with the anodal electrode generally increases motor cortex excitability, whereas cathodal electrode stimulation produces the opposite effect [60]. tDCS can also promote changes in synaptic plasticity by increasing the expression of the brain-derived neurotrophic factor [61]. The duration of the stimulation session is also important, as it must be sufficient to induce these changes [62]. The primary mechanism of tDCS is thought to be the enhancement of long-term synaptic plasticity [62, 63].

In our study, we believe it is not appropriate to compare the results of rTMS with tDCS studies. These are independent articles with distinct methodologies, differing patient characteristics, and varied stimulation parameters, such as the stimulated area and study duration. The differences in their effects on motor and gait assessments can be attributed to their unique stimulation techniques and fundamentally different mechanisms of action. Additionally, significant variability in the number of studies analyzed and the baseline conditions of participants may have further influenced the reported effectiveness of each technique.

rTMS operates via electromagnetic induction, generating electrical currents that affect nearby cells. At high frequency, rTMS stimulates projection neurons [64], while at low frequency, it predominantly impacts inhibitory interneurons [64, 65]. Unlike tDCS, rTMS penetrates deep into the brain tissue, reaching areas otherwise inaccessible to other stimulation methods.

In contrast, tDCS involves passing a weak current (1–2.5 mA) through surface electrodes [66], inducing excitability changes across broad cortical areas [67, 68]. This technique has recently garnered attention due to its cost-effectiveness, portability, and ease of use compared to other stimulation methods like rTMS [66, 69]. The effects of tDCS depend heavily on factors such as intensity, electrode type and placement, and application duration. Moreover, studies have highlighted significant interindividual variability in response to tDCS [70].

Although meta-analysis could not be conducted for the non-invasive spinal cord stimulation category, the tsDCS study [46] did not show any improvement in LEMS score. However, it is important to note that the sample size was very small, with only 3 subjects. In contrast, the study that used tSCS [47] reported a significant improvement in walking speed.

In the one study that used tSCS, stimulation was applied over thoracic vertebra 11–12 at 50 Hz, with a biphasic current for 30 min, with the tSCS group showing a significant improvement in walking speed [37]. This stimulation involves the delivery of electrical impulses at a high intensity to the spinal cord via transcutaneous electrodes placed over the vertebrae. These impulses promote the activation of neural networks within the spinal cord, potentially through the recruitment of afferent fibres to the posterior root [33, 71, 72]. While tSCS provides rests within the wave type, in tsDCS, the current is direct, and the intensity is generally set at 2–2.5 mA with no rests in its application [30]. tSCS is a novel technique and it needs further investigation beyond this one RCT

to better determine its clinical usefulness. tSCS does not directly produce action potentials but promotes spinal network excitability through the activation of inaccessible interneuronal networks in the posterior roots of the spinal cord [33, 71, 72]. The excitability of these networks around the lesion level may amplify voluntary control and facilitate neural reorganization [32].

As previously described, non-invasive central nervous system stimulation techniques differ greatly in terms of their level, parameters and effects. This variation should be carefully considered, and we recommend that future research avoid comparing different techniques directly, as it has been shown that a pooled analysis does not correlate with the results from each technique independently [14, 73, 74].

Limitations

This investigation presents some limitations, the first being the availability of data. Availability, presentation and access to complete information from the studies was uneven, so potential data which may have contributed to the robustness of the results could not be incorporated. Also, we included only articles published in English and Spanish, which may introduce bias if relevant studies have been published in other languages.

Secondly, there was a big variability of datasets. A larger quantity of studies showed interesting data compared to those who were finally included in the statistical metanalysis. The data from those studies was mostly incomplete (just assessed once) or presented in different ways rendering it impossible to undergo a statistical comparative analysis.

Third, contributing to the changeability of data, the total number of participants in each study displayed a wide range of variability (from 12 to 43). Also, age was distributed unevenly, as well as time since injury (from 2.5 months up until 5.2 years) and neurological level of injury (C2-L2) and AIS category (A, B, C, D). This contributes to the variability of results within and between studies.

Finally, our results are restricted to the short-term effects of the interventions, as the included studies either did not assess long-term follow-up, or when follow-up was completed the variations in the time to completion was too large between studies (i.e. from 2 up until 8 weeks). Future research should address this aspect to provide a more standardized approach.

Conclusions

When pooled, non-invasive stimulation techniques showed significant effects on motor strength and gait function. However, subgroup analyses revealed reduced effects, particularly for rTMS and tDCS, and a lack of studies prevented meta-analysis for non-invasive spinal cord stimulation (tsDCS and tSCS). More randomized controlled trials are needed to validate neuromodulation interventions, especially non-invasive spinal cord stimulation, for motor and gait recovery in SCI.

This review underscores the importance of standardized motor, gait, and functional recovery measures, as well as follow-up evaluations, to assess long-term efficacy. Future studies should include comprehensive data, such as means and standard deviations, to enhance consistency, comparability, and interpretation of results.

Abbreviations

10MWT	10 Metres Walking Test
2mWT	2 Metres Walking Test
6MWT	6 Minutes Walking Test
AIS	Abbreviated Injury Scale
BT	Balance training
BWSTT	Bodyweight supported treadmill training
C	Cervical
CPG	Central pattern generator
EBE	Evidence-based exercise
FES	Functional electrical stimulation
GT	Gait training
iTBS	Intermittent Theta Burst Stimulation
L	Lumbar
LEMS	Lower Extremity Motor Scale
LT	Locomotor Training
MAS	Modified Ashworth Scale
MST	Motor skill training
NA	Not available
NIBS	Non-invasive brain stimulation
NISCS	Non-invasive spinal cord stimulation
PEDro	Physiotherapy evidence database
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
PT	Physical training
RAGT	Robot-assisted gait training
RCT	Randomized control trial
RMT	Resting motor threshold
rTMS	Repetitive Transcranial Magnetic Stimulation
SCI	Spinal cord injury
SD	Standard deviation
ST	Strength training
T	Thoracic
tDCS	Transcranial direct current stimulation
TMS	Transcranial magnetic stimulation
tSCS	Transcutaneous spinal cord stimulation
tsDCS	Transcutaneous spinal direct current stimulation
TSI	Time since injury
TUG	Timed up and go test
tvDCS	Transvertebral direct current stimulation
WISCI	Walking Index Spinal Cord Injury

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Author contributions

HK concepted the study design. AHN, ARA, MY and MW performed the search and retrieved the results. ARA, MY and AHN collected the data. HK and AHN contributed to data interpretation and writing of the manuscript.

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Availability of data and materials
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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