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Review Article

A Review of Functional Restoration From Spinal Cord Stimulation in Patients With Spinal Cord Injury

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Traumatic spinal cord injury often leads to loss of sensory, motor, and autonomic function below the level of injury. Recent advancements in spinal cord electrical stimulation (SCS) for spinal cord injury have provided potential avenues for restoration of neurologic function in affected patients. This review aims to assess the efficacy of spinal cord stimulation, both epidural (eSCS) and transcutaneous (tSCS), on the return of function in individuals with chronic spinal cord injury. The current literature on human clinical eSCS and tSCS for spinal cord injury was reviewed. Seventy-one relevant studies were included for review, specifically examining changes in volitional movement, changes in muscle activity or spasticity, or return of cardiovascular pulmonary, or genitourinary autonomic function. The total participant sample comprised of 327 patients with spinal cord injury, each evaluated using different stimulation protocols, some for sensorimotor function and others for various autonomic functions. One hundred eight of 127 patients saw improvement in sensorimotor function, 51 of 70 patients saw improvement in autonomic genitourinary function, 32 of 32 patients saw improvement in autonomic pulmonary function, and 32 of 36 patients saw improvement in autonomic cardiovascular function. Although this review highlights SCS as a promising therapeutic neuromodulatory technique to improve rehabilitation in patients with SCI, further mechanistic studies and stimulus parameter optimization are necessary before clinical translation.

Keywords: Spinal cord injury, Spinal cord stimulation, Electrical stimulation

INTRODUCTION

Spinal cord injury (SCI) is a destructive neurological state with complex pathophysiologic consequences. SCI often occurs secondary to trauma that leads to loss of sensory, motor, and/or autonomic functions.[1,2] The initial mechanical injury to the spinal cord causes damage to neural parenchyma, disruption of axonal networks, and glial membrane disruption, collectively known as primary injury.[1] Following this initial insult, secondary damage to the injured spinal cord may occur via apoptotic signaling, ischemia, excitotoxicity, inflammation, and axonal demyelination. Glial scar formation often develops as a result of these local events, which can impair axonal regeneration and synaptic neuroplasticity across the injury site.[3] Although there have been several improvements in the understanding of SCI pathophysiology and clinical care, there is no cure for SCI, and the current standard of treatment focuses on teaching compensation strategies to mitigate losses of function.

Recent research has demonstrated novel methods to improve post-SCI recovery and reverse the deleterious outcomes of SCI. Most cases of SCI have an intervening gap of intact tissue at the site of injury; while this tissue is anatomically intact, it is functionally silent due to disruptions to the flow of information within the spinal cord.[4] Upper motor neurons lose the feedback of

afferent signals and the descending efferent signals terminate at the level of the SCI lesion, though in some cases, propriospinal connections can still provide indirect access to afferent signals.[5,6] Recent research has indicated that functional recovery can be achieved by taking advantage of the remaining neural connections to re-enable sensorimotor function.[7] In mouse models, Courtine et al.[5] show functional recovery of propriospinal relay connections can only occur when spatially separated lateral hemisections are also separated temporally (i.e., when spinal hemisections were delivered 10 weeks apart), indicating the "rewiring" of connections following SCI via neural plasticity. Circuit reconstruction involves not just the growth of new nerves, but also synaptic regeneration and axonal regrowth to strengthen pre-existing sensorimotor networks.[8,9] The spontaneous formation of new synapses from local surviving terminals or distant axons occurs in neural tissue that has been spared but is responding to injury. Appropriate axonal growth can be stimulated by growth factors or genetic activation; in rats, growth cone formation and axon regeneration may improve with changes to the axonal cytoskeleton.[10,11] By modulating the microenvironment of an injury to increase synaptic regeneration or axonal regrowth, damaged neural circuits can potentially be reconstructed with variable functionality.

One technique that has recently grown in prominence for functional recovery in chronic SCI patients is the use of chronic electrical stimulation of the spinal cord. Use of spinal cord stimulation (SCS) on the lumbosacral spinal cord of individuals clinically diagnosed with chronic, motor complete SCI has demonstrated restoration of a wide range of functions. The impact of long-term implantation remains unknown and requires further study along with factors such as injury level and grade, stimulation parameters, and associated pharmacology and physical therapy, which may lead to greater efficacy. The restorative power of adjunctive SCS is likely enabled by the remaining propriospinal fibers that support plasticity by enabling communication across the spinal cord lesion. Animal and computational models have suggested that SCS may recruit nearby Group I and II afferent fibers which excite myelinated motor neurons through monosynaptic and/or polysynaptic pathways.[12-15] In rodent models, transformation from dormant to active tissue at the injury site occurs through increasing the general level of excitability, allowing sensory information to become a source of control for voluntary movement; using sensory information as a source of control requires an extensive amount of physical training to allow for appropriate remodeling of supraspinal and intraspinal pathways.[16] Further study of electrical stimulation for functional recovery in human patients with chronic SCI is necessary to determine the efficacy of such treatments and to translate electrical stimulation from basic research to effective clinical use.

The aim of this review is to discuss the efficacy and safety of SCS as a neuromodulatory strategy for restoration of neurologic function in patients with chronic SCI. Previous work has been performed to survey the scientific literature regarding the effects of SCS in SCI, however these reviews have focused on either eSCS or tSCS and their effects on a limited number of physiological systems.[17] Here, we discuss the reported effects of SCS, both epidural spinal cord stimulation (eSCS) and transcutaneous spinal cord stimulation (tSCS), on sensory, motor, autonomic, cardiovascular, and pulmonary systems. Finally, we review the limitations of the current literature, and future directions for research in this promising area. This review indicates that eSCS and tSCS are efficacious and safe treatments for chronic SCI, with the potential to improve motor and autonomic function following SCI, but further work needs to be performed to define what patients will respond most efficaciously to either eSCS or tSCS therapy.

METHODS

1. Search Strategy

To undertake this review, we followed a protocol in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.[18] A search was made of the following electronic databases: PubMed, Cochrane Registry, Embase, and OVID. For the search, we used keywords *spinal cord injury*, *spinal cord stimulation, epidural stimulation, transcutaneous magnetic stimulation, motor control, movement, and rehabilitation,* combined in the databases as follows: ("spinal cord injury") AND ("spinal cord stimulation" OR "epidural stimulation" OR "spinal cord stimulator" OR "epidural stimulator" OR "Electrodes, Implanted" OR "paddle spinal cord stimulator" OR "implantable electrodes" OR "transcutaneous magnetic stimulation" OR "Spinal Cord Injuries/therapy*" OR "Spinal Cord Stimulation/methods*") AND ("motor control" OR "movement" OR "rehabilitation"). The search was conducted from the start dates of each respective database until January 1st, 2022. Additionally, we carried out an inverse search of the references cited by any relevant articles.

2. Selection Criteria

Using the PICOS structure (Patients, Intervention, Comparison, Outcome, and Study design), we established the following

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inclusion criteria, requiring (1) human patients to have SCI, (2) electrical spinal stimulation to be applied, and (3) outcomes to include assessment of response. We excluded articles that (1) used spinal stimulation for chronic pain treatment and (2) present secondary data, such as literature reviews. Studies performing retrospective analysis on data collected while routinely conducting clinical protocols for evaluation of SCS for spasticity or chronic pain treatment were included. The selection of articles was decided by 2 independent researchers (AL and ES) working in parallel with no points of disagreement.

3. Study Selection

The process for selecting articles was as follows: (1) any duplicates of studies found in the various databases were eliminated; (2) after an initial screening of titles, the abstracts were read to identify articles that fulfilled the pre-established inclusion criteria; and (3) the full text of the remaining studies was read, with any studies meeting the exclusion criteria being ruled out. Researchers worked in parallel to extract data, including subject demographics and injury information as well as SCS stimulation parameters and post-SCS outcomes. Given the possibility of enrollment in multiple studies, for the sake of our review, we treated each patient enrolled in a study to be independent of other patients and other studies. For clinical trials including control groups, we excluded patients in the control groups from our analyses.

4. Bias Assessment

The risk of bias was assessed by 2 independent researchers (AL and ES) using the Risk of Bias in Non-Randomized Studies of Interventions (ROBINS-I) tool by the Cochrane Scientific Committee for nonrandomized studies of effects of interventions. A detailed description of the process can be found in the Supplementary Table 1.

RESULTS

A total of 503 research reports were located in the above databases. After eliminating duplicates and screening of titles and abstracts, 50 reports were selected for a full reading of the text. After full reading, 12 articles were excluded, and 33 additional studies were identified through the review of bibliographic references. Finally, 71 studies were included in the review. The study selection process can be seen in Fig. 1.

The study design and characteristics of participants are shown in Table 1. Of the reports included in the review, 50 were case or case-series studies[2,7,19-66] and 21 were clinical trials.[67-88] The total study sample comprised of 327 patients with SCI, 257 males, 54 females, and 16 participants where sex was not specified. Patient age ranged from 18 to 66 years old. The time since injury ranged from 0.1 to 41.1 years. The majority of patients had injury levels in the cervical (n = 174 patients) and thoracic (n = 106 patients) regions. The highest reported level of injury was at C1

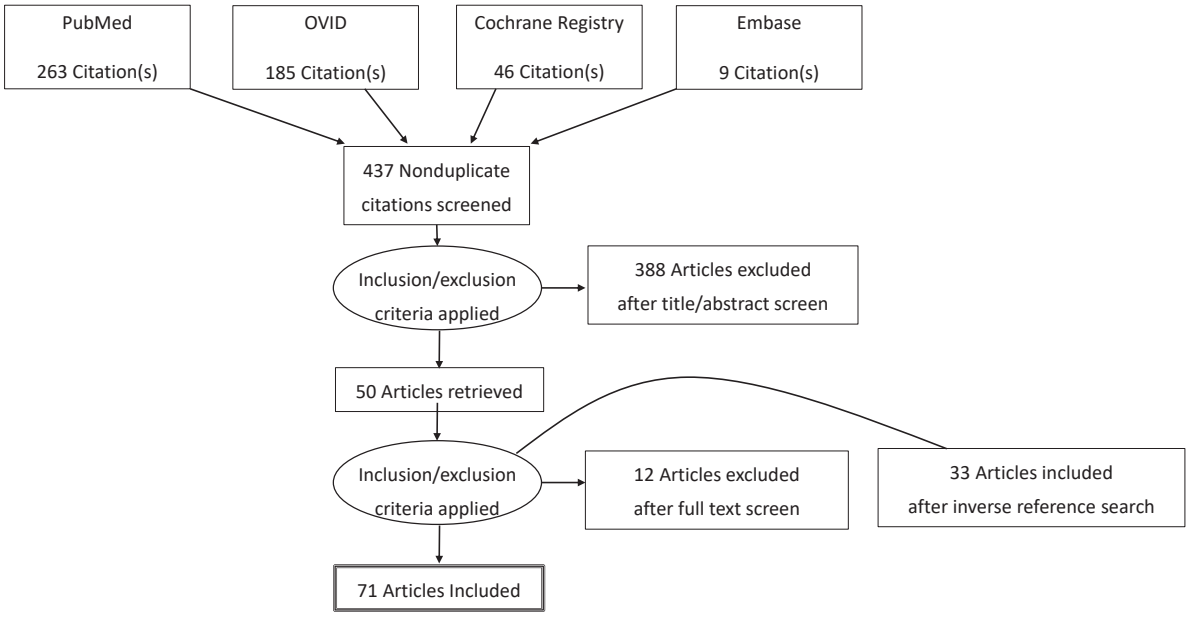

Fig. 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram of search for systematic review.[2,7,19-88]

Table 1. Study designs, demographic and clinical characteristics of patients with spinal cord injury enrolled in studies evaluating spinal cord stimulation for restoration of function

Study	Design	Site	Subjects (n)	Sex	Age (yr), mean ± SD	Age (yr), range	Level of injury	AIS	Time (yr), mean ± SD	SCI length (yr), range
Barolat et al.[19] (1986)	Case report	Philadelphia, PA, USA	1	M	22	22	C5	C	0.75	0.75
Katz et al.[20] (1991)	Case series	Richmond, VA, USA	33	31M, 2F	-	24–66	C4–T10	A–D	-	0.6–31.5
Herman et al.[21] (2002)	Case report	Phoenix, AZ, USA	1	M	43	43	C6	C	3.5	3.5
Carhart et al.[22] (2004)	Case report	Phoenix, AZ, USA	1	M	43	43	C5–C6	C	3.5	3.5
Jilge et al.[23] (2004)	Case series (retrospective)	Vienna, Austria	5	2M, 3F	27.6 ± 3.4	24–34	C4–T10	4A, 1B	4.8 ± 3.4	2–8
Minassian et al.[24] (2004)	Case series (retrospective)	Vienna, Austria	10	7M, 3F	26.9 ± 11.7	18–58	C4–T10	8A, 2B	2.7 ± 1.3	1–5
Ganley et al.[25] (2005)	Case series	Tempe, AZ, USA	2	2M	45.4 ± 2.5	43–48	C6–T8	C	5.8 ± 2.3	3.5–8.0
DiMarco et al.[26] (2006)	Case report	Cleveland, OH, USA	1	M	52	52	C5–C6	C	7	7
Huang et al.[27] (2006)	Case series	Tempe/Phoenix, AZ, USA	2	2M	45.5 ± 3.5	43–48	C5–T8	C	5.8 ± 3.2	3.5–8
DiMarco et al.[67,68] (2009)	Clinical trial	Cleveland, OH, USA	9	8M, 1F	41 ± 11.5	23–52	C3–C6	-	13.1 ± 11.3	1–34
Harkema et al. (2011)[28]	Case report	Louisville, KY/Los Angeles, CA, USA	1	M	23	23	C7	B	3	3
Moshonkina et al.[29] (2012)	Case series	St. Petersburg, Russia	4	1M, 3F	42 ± 15.7	22–58	C5–L1	2A/B, 1B, 1B/C	-	-
Hofstoetter et al.[30] (2013)	Case report	Vienna, Austria	1	F	29	29	T9	D	11	11
Angeli et al.[7] (2014)	Case series	Louisville, KY/Los Angeles, CA, USA	4	4M	26.9 ± 4	23–32	C6–T6	2A, 2B	3.0 ± 1	2.2–4.2
Hofstoetter et al.[31] (2014)	Case series	Vienna, Austria	3	2M, 1F	32.7 ± 4.1	28–38	C5–T9	D	10.6 ± 1.5	9–12
Sayenko et al.[32] (2014)	Case series	Louisville, KY/Los Angeles, CA, USA	3	3M	26.3 ± 4.9	23–32	C7–T4	1A, 2B	3.3 ± 1.0	2.2–4.2
Bedi and Arumugam[33] (2015)	Case report	Punjab, India	1	M	25	25	L1	C	2.5	2.5
Gerasimenko et al.[34] (2015)	Case series	St. Petersburg, Russia/Los Angeles, CA, USA	5	-	-	-	-	-	-	-
Hofstoetter et al.[35] (2015)	Case series	Vienna, Austria	3	2M, 1F	32.6 ± 5.0	28–38	C5–T9	D	10.6 ± 1.5	9–12
Rejc et al.[36] (2015)	Case series	Louisville, KY/Los Angeles, CA, USA	4	4M	27 ± 4.2	24–33	C7–T4	2A, 2B	3.0 ± 1	2.2–4.2
Bedi and Arumugam[37] (2016)	Case report	Punjab, India	1	M	25	25	T12	C	-	-
Lu et al.[38] (2016)	Case series	Los Angeles, CA, USA	2	2M	19 ± 1	18–20	C5–C6	B	2.3 ± 0.4	2–2.5
Minassian et al.[39] (2016)	Case series	Vienna, Austria	4	3M, 1F	39.5 ± 17.1	26–64	C8–T8	A	3.5 ± 1.7	1.7–4.8
Gad et al.[40] (2017)	Case report	Los Angeles, CA, USA	1	M	40	40	T9	A	4	4

(*Continued*)

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Table 1. Study designs, demographic and clinical characteristics of patients with spinal cord injury enrolled in studies evaluating spinal cord stimulation for restoration of function (continued)

Study	Design	Site	Subjects (n)	Sex	Age (yr), mean ± SD	Age (yr), range	Level of injury	AIS	Time (yr), mean ± SD	SCI length (yr), range
Grahn et al.[41] (2017)	Case report	Rochester, MN, USA	1	M	26	26	T6	A	3	3
Rejc et al.[42] (2017)	Case report	Louisville, KY/Los Angeles, CA, USA	1	M	32	32	C7	B	4.2	4.2
Rejc et al.[43] (2017)	Case series	Louisville, KY/Los Angeles, CA, USA	4	4M	27 ± 4.2	24–33	C7–T4	2A, 2B	3.0 ± 1	2.2–4.2
Angeli et al.[44] (2018)	Case series	Louisville, KY, USA	4	3M, 1F	25.8 ± 4.5	22–32	C5–T4	2A, 2B	3.1 ± 0.4	2.2–3.3
Aslan et al.[45] (2018)	Case series	Louisville, KY, USA	7	7M	26.7 ± 4.1	-	C5–T4	4A, 3B	2.7 ± 0.5	2.0–3.5
DiMarco et al.[46] (2018)	Case report	Cleveland, OH, USA	1	M	50	50	C4	-	2	2
Formento et al.[47] (2018)	Case series	Laussane, Switzerland	3	3M	36.7 ± 9.6	28–47	C4–C7	2C, 1D	5.3 ± 1.2	4–6
Freyvert et al.[69] (2018)	Clinical trial	Los Angeles, CA, USA	6	4M, 2F	19.1 ± 1.3	18–21	C2–C6	B	2.3 ± 0.9	1.5–3.8
Gad et al.[70] (2018)	Clinical trial	Los Angeles, CA, USA	6	5M, 1F	40.2 ± 16.6	20–62	C4–C8	2B, 4C	10.0 ± 7.1	1.1–21
Gill et al.[48] (2018)	Case report	Rochester, MN, USA	1	M	26	26	T8	A	3	3
Harkema et al.[71] (2018a)	Clinical trial	Louisville, KY, USA	4	3M, 1F	30.8 ± 4.1	24–35	C4	3A, 1B	6.5 ± 1.6	3.8–8
Harkema et al.[72] (2018b)	Clinical trial	Louisville, KY, USA	4	3M, 1F	30.8 ± 4.1	24–35	C4	3A, 1B	6.5 ± 1.6	3.8–8
Herrity et al.[49] (2018)	Case series	Louisville, KY, USA	5	5M	-	-	C4–C5, T4	3A, 2B	5.9 ± 1.9	-
Inanici et al.[73] (2018)	Clinical trial	Seattle, WA, USA	1	M	62	62	C3–C4	D	2	2
Niu et al.[74] (2018)	Clinical trial	Los Angeles, CA, USA	5	5M	31 ± 10.6	22–43	C5–T4	A-B	8.8 ± 7.5	5–13
Phillips et al.[50] (2018)	Case series	Los Angeles, CA, USA	5	-	-	-	C5–T2	3A, 2B	> 3	> 3
Powell et al.[51] (2018)	Case series	Louisville, KY, USA	6	4M, 2F	45.8 ± 14	26–59	C6–L1	4C, 2D	15.7 ± 13.4	4.6–41.1
Rath et al.[52] (2018)	Case series	Los Angeles, CA, USA	8	7M, 1F	29.4 ± 7.7	23–47	C4–T9	6A, 2C	7.3 ± 3.3	2–13
Wagner et al.[2] (2018)	Case series	Laussane, Switzerland	3	3M	36.7 ± 9.6	28–47	C4–C8	2C, 1D	5.3 ± 1.2	4–6
Walter et al.[53] (2018)	Case report	Vancouver, BC, Canada	1	M	32	32	C5	B	6	6
West et al.[54] (2018)	Case report	Vancouver, BC, Canada	1	M	Early 30s	Early 30s	C5	B	-	-
Calvert et al.[75] (2019)	Clinical trial	Rochester, MN, USA	2	2M	31.5 ± 7.8	26–37	T3–T6	A	4.5 ± 2.1	3–6
Cheng et al.[55] (2019)	Case series	Pasadena, CA/Louisville, KY, USA	2	-	-	-	-	A	-	–
Darrow et al.[76] (2019)	Clinical trial	Minneapolis, MN, USA	2	2F	50 ± 2.8	48–52	T4–T8	A	7.5 ± 3.5	5–10
Knikou et al.[56] (2019)	Case series	New York, NY, USA	10	7M, 3F	36.3 ± 11.2	19–51	C6–T12	2A, 2B, 1C, 5D	8.8 ± 8.1	2–28
Nightingale et al.[57] (2019)	Case report	Vancouver, BC, Canada	1	M	33	33	C5	B	5	5
Sayenko et al.[77] (2019)	Clinical trial	Los Angeles, CA, USA	15	12M, 3F	31.2 ± 8.7	23–53	C4–T12	11A, 1B, 3C	6.0 ± 3.2	2–13

(*Continued*)

Table 1. Study designs, demographic and clinical characteristics of patients with spinal cord injury enrolled in studies evaluating spinal cord stimulation for restoration of function (continued)

Study	Design	Site	Subjects (n)	Sex	Age (yr), mean ± SD	Age (yr), range	Level of injury	AIS	Time (yr), mean ± SD	SCI length (yr), range
Terson de Paleville et al.[58] (2019)	Case series	Louisville, KY, USA	4	4M	27.3 ± 3.7	22.7–31.6	C5–T5	3A, 1B	2.6 ± 0.3	2.3–2.9
Alam et al.[78] (2020)	Clinical trial	Hong Kong, China	1	F	48	48	C7	-	21	21
DiMarco et al.[59] (2020)	Case series	Cleveland, OH, USA	10	10M	40.4 ± 12.1	27–58	C2–T1	-	7.1 ± 10.7	3–37
Gad et al.[60] (2020)	Case report	Los Angeles, CA, USA	1	M	39	39	C5	A	9	9
Gill et al.[79] (2020)	Clinical trial	Rochester, MN, USA	2	-	31.5 ± 7.8	26–37	T3–T6	A	4.5 ± 2.1	3–6
Gorgey et al.[80] (2020)	Clinical trial	Richmond, VA, USA	1	1M	26	26	C7	C	2	2
Peña Pino et al.[81] (2020)	Clinical trial	Minneapolis, MN, USA	7	4M, 3F	42 ± 11.4	30–60	T4–T8	6A, 1B	7.7 ± 4.8	3–17
Wiesener et al.[61] (2020)	Case series	Berlin, Germany	2	-	49 ± 12.7	40–58	T5–T6	A	23 ± 18.4	10–36
Wu et al.[82] (2020)	Clinical trial	Bronx, NY, USA	9	7M, 2F	45.9 ± 13.7	22–64	C2–C8	1B, 4C, 4D	10.8 ± 5.9	1–17
Beck et al.[62] (2021)	Case series	Rochester, MN, USA	2	2M	31.5 ± 5.5	26–37	T3–T6	A	4.5 ± 1.5	3–6
Calvert et al.[63] (2021)	Case series	Los Angeles, CA/Rochester, MN, USA	9	8M, 1F	27.1 ± 4.1	22–36	C5–T6	5A, 1B, 3C	6.1 ± 3.1	2–13
DiMarco et al.[83] (2021)	Clinical trial	Cleveland, OH, USA	5	5M	-	30–50	C3–T1	A	-	2–4
Estes et al.[84] (2021)	Clinical trial	Atlanta, GA, USA	8	6M, 2F	44.4 ± 15.7	18–63	C1–C7	2C, 6D	0.3 ± 0.1	0.1–0.5
Herrity et al.[85] (2021)	Clinical trial	Louisville, KY, USA	10	8M, 2F	27.9 ± 4.7	20–51	C3–T4	6A, 4B	4.4 ± 2.3	1–15
Ibáñez et al.[64] (2021)	Case series	Louisville, KY, USA	5	5M	31.9 ± 10.7	24–52	C4–T4	3A, 2B	7.8 ± 5.2	2.2–16.6
Inanici et al.[86] (2021)	Clinical trial	Seattle, WA, USA	6	4M, 2F	42 ± 14	28–62	C3–C5	2B, 2C, 2D	4.6 ± 3.8	1.5–12
Linde et al.[87] (2021)	Clinical trial	Rochester, MN, USA	2	2M	31.5 ± 5.5	26–37	T3–T6	A	4.5 ± 1.5	3–6
Mesbah et al.[65] (2021)	Case series	Louisville, KY, USA	20	15M, 5F	31.0 ± 9.6	19.9–60.6	C3–T4	14A, 6B	6.3 ± 3.4	2.4–16.6
Squair et al.[66] (2021)	Case report	Calgary, Alberta, Canada	1	M	38	38	C5	A	1	1
Smith et al.[88] (2022)	Clinical trial	Louisville, KY, USA	11	8M, 3F	-	21–45	C2–T1	6A, 5B	5.1 ± 2.2	2.4–8.6

SD, standard deviation; AIS, American Spinal Injury Association Impairment Scale.

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Table 2. Stimulation parameters of selected studies for epidural spinal cord stimulation facilitation of outcomes following spinal cord injury

Study	Intervention	Stimulator type	Lead placement	No. of electrodes/lead	Stimulation parameters	Location	Stimulation frequency	Stimulation pulse width	Stimulation amplitude	Stimulation pattern	Stimulation optimization
Barolat et al.[19] (1986)	eSCS	Clinical technology corporation	Percutaneous	1	Tonic stimulation	T1–T2	75 Hz	250 μs	-	-	-
Katz et al.[20] (1991)	eSCS	Medtronic	Paddle	4	Tonic stimulation	-	-	-	-	-	Parameters optimized for spasticity
Herman et al.[21] (2002)	eSCS+BWST therapy	Medtronic	Percutaneous	4	Tonic stimulation	Lumbar enlargement	-	-	-	-	A variety of electrical parameter sets were examined
Carhart et al.[22] (2004)	eSCS+PWBT therapy	Medtronic	Percutaneous	4	Tonic stimulation	T10–T12	40–60 Hz	800 μs	Amplitude at midpoint between sensory and motor threshold values	Continuous, charge-balanced, monophasic pulse trains	-
Jilge et al.[23] (2004)	eSCS	Medtronic	Percutaneous	4	Tonic stimulation	T12–L1	5–60 Hz	210–450 μs	1-10 V	Pulse trains	-
Minassian et al.[24] (2004)	eSCS	Medtronic	Percutaneous	4	Tonic stimulation	T10–T12	2.2–50 Hz	-	1-10 V	Single pulse, paired pulses, and pulse trains	-
Ganley et al.[25] (2005)	eSCS+ locomotor training	-	Percutaneous	4	Tonic stimulation	T10–T12	20–60 Hz	800 μs	Amplitudes between sensory and motor thresholds in S1 and at motor threshold for S2	-	Adjusted on an individual basis
DiMarco et al.[26] (2006)	eSCS	NeuroControl	Percutaneous	1	Tonic stimulation	T9, T11, L1	53 Hz	150 μs at T9, 200 ms at T11 and L1	40 V	Pulse train with stimulation trigger controlled by patient	-
Huang et al.[27] (2006)	eSCS+partial weight bearing treadmill therapy	Medtronic	Percutaneous	4	Tonic stimulation	T10–L2	20–40 Hz	800 μs	3-8.5 V	Pulse train	-
DiMarco et al.[67,68] (2009)	eSCS	-	Percutaneous	1	Tonic stimulation	T9, T11, L1	30–40 Hz	150–200 μs	30-40 V	Pulse train	-
Harkema et al.[28] (2011)	eSCS+stand training	Medtronic	Paddle	16	Tonic stimulation	L1–S1	Stimulation for standing caudal L5–S1 at 15 Hz; stimulation for manually facilitated stepping: 30–40 Hz	210 or 450 μs	7.5 V	Different stimulation protocols for different activities: both involve tonic stimulation.	-

(*Continued*)

Table 2. Stimulation parameters of selected studies for epidural spinal cord stimulation facilitation of outcomes following spinal cord injury (continued)

Study	Intervention	Stimulator type	Lead placement	No. of electrodes/lead	Stimulation parameters	Location	Stimulation frequency	Stimulation pulse width	Stimulation amplitude	Stimulation pattern	Stimulation optimization
Moshonkina et al.[29] (2012)	eSCS+ locomotor training	Cooner Wire Co.	Percutaneous	2-4	Tonic stimulation	L2–L4, S2	1–12 Hz	-	-	Carried out 2 times for 30 min in addition to the routine pharmacotherapy	-
Angeli et al.[7] (2014)	eSCS+ locomotor training	Medtronic	Paddle	16	Tonic stimulation	L1–S1	25–30 Hz	-	-	-	Stimulation parameters optimized to target primary motor pool activation areas.
Sayenko et al.[32] (2014)	eSCS	Medtronic	Paddle	16	Tonic stimulation	L1–S2	2 Hz	210 μs	0.5-10 V	Spatially selective, rectangular, biphasic pulse waveform	All modified for individual patients
Rejc et al.[36] (2015)	eSCS+ locomotor training	Medtronic	Paddle	16	Tonic stimulation	L1–S1	25–60 Hz	-	1.0-9.0 V	-	Adjustments made to electrode configurations to activate specific motor neuron pools
Lu et al.[38] (2016)	eSCS	Boston Scientific	Paddle	16	Tonic stimulation	C4/C5–T1	2–40 Hz	210 μs	0.1-10.0 mA	Biphasic stimulation	Optimized for greatest hand motor responses
Grahn et al.[41] (2017)	eSCS+ locomotor training	Medtronic	Paddle	16	Tonic stimulation	Lumbar enlargement	-	-	-	-	Active electrode configurations and stimulation parameters were adjusted to allow volitional control.
Rejc et al.[42] (2017)	eSCS+ locomotor training	Medtronic	Paddle	16	Tonic stimulation	L1–S1	Stimulation for standing: 40-60 Hz at T1–T2, T3–T8. Stimulation for stepping: 30–55 Hz at T2–T3, T5–T6, T7–T9. Stimulation for voluntary movement: 30–65 Hz at T1–T3.	-	Stimulation for standing: 0.6–1.0 V at T1–T2, T3–T8. Stimulation for stepping: 0.7-3.5V at T2–T3, T5–T6, T7-T9. Stimulation for voluntary movement: 0.4–2.2 V at T1–T3.	-	Varied electrode configuration for left/right side and specific activities.
Rejc et al.[43] (2017)	eSCS+ locomotor training	Medtronic	Paddle	16	Tonic stimulation	L1–S1	Starting stimulation parameters of frequency 2 Hz	-	0.1-5 V	-	Parameters modulated synergistically to find stimulation frequency that elicited continuous (non-rhythmic) EMG pattern.
Angeli et al.[44] (2018)	eSCS+ locomotor training	Medtronic	Paddle	16	Tonic stimulation	L1–S1/S2	2 Hz	450 μs	0.1 V ramping incrementally	-	Stimulation configurations selected to promote standing or stepping.

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Table 2. Stimulation parameters of selected studies for epidural spinal cord stimulation facilitation of outcomes following spinal cord injury (continued)

Study	Intervention	Stimulator type	Lead placement	No. of electrodes/lead	Stimulation parameters	Location	Stimulation frequency	Stimulation pulse width	Stimulation amplitude	Stimulation pattern	Stimulation optimization
Aslan et al.[45] (2018)	eSCS	Medtronic	Paddle	16	Tonic stimulation	T11–L1	-	-	-	-	In standing experiments, voltage, frequency, and configuration of the electrode array were unique to each participant and optimized for over-ground standing.
DiMarco et al.[46] (2018)	eSCS	-	Percutaneous	2	Tonic stimulation	T9, T11	50 Hz	0.2 ms	40 V	Pulse train with monopolar stimulation at T9 or bipolar stimulation at T9/T11	
Formento et al.[47] (2018)	eSCS	Medtronic	Paddle	16	Tonic stimulation	Lumbosacral	40 Hz	-	3–9 mA	-	Spatially specific stimulation parameters optimized to target primary motor pool activation areas that were key in movement.
Gill et al.[48] (2018)	eSCS+ locomotor training	Medtronic	Paddle	16	Tonic stimulation	T11–L1	15–40 Hz	210 μs	-	Biphasic, charge-balanced pulses	Parameters modified to enable voluntary control.
Harkema et al.[71] (2018)	eSCS	Medtronic	Paddle	16	Tonic stimulation	T11–L1	-	450 μs	-	-	Configurations (anode and cathode electrode selection, voltage, frequency) were identified to maintain systolic blood pressure within the desired range, then adjusted as needed.
Harkema et al.[72] (2018)	eSCS	Medtronic	Paddle	16	Tonic stimulation	T11–L1	-	450 μs	-	-	Configurations (anode and cathode electrode selection, voltage, frequency) were identified to maintain systolic blood pressure within the desired range, then adjusted as needed.
Herrity et al.[49] (2018)	eSCS+activity-based recovery training	Medtronic	Paddle	16	Tonic stimulation	L1–S1	30 Hz	450 μs	Voltage was ramped up slowly (0.1 V increments)	-	All stimulation at the lower end of the stimulator array optimized for a single patient, then carried over to other patients

(*Continued*)

Table 2. Stimulation parameters of selected studies for epidural spinal cord stimulation facilitation of outcomes following spinal cord injury (continued)

Study	Intervention	Stimulator type	Lead placement	No. of electrodes/lead	Stimulation parameters	Location	Stimulation frequency	Stimulation pulse width	Stimulation amplitude	Stimulation pattern	Stimulation optimization
Wagner et al.[2] (2018)	eSCS+ locomotor training+ gravity assist device	Medtronic	Paddle	16	Spatiotemporal modulation	T11–L1	20–60 Hz	-	-	Trains of spatially selective stimulation with timing that coincided with intended movement	-
Walter et al.[53] (2018)	eSCS	Medtronic	Paddle	16	Tonic stimulation	T11–L1	-	-	-	Trains of spatially selective stimulation with timing for specific actions pre-programmed	Participant could adjust intensity of program manually as needed
West et al.[54] (2018)	eSCS	Medtronic	Paddle	16	Tonic stimulation	T11–L1	35 Hz	300 μs	3.5 V	-	-
Calvert et al.[75] (2019)	eSCS+ locomotor training	Medtronic	Paddle	16	Tonic stimulation	T11–L1	40 Hz	210 μs	-	Trains of spatially selective stimulation with timing for specific actions	-
Cheng et al.[55] (2019)	eSCS+stand training	Medtronic	Paddle	16	Tonic stimulation	L1–S1	25 Hz	200 μs			Stimuli optimized with machine learning algorithm
Darrow et al.[76] (2019)	eSCS	Abbott	Paddle	16	Tonic stimulation	L1–S2	16–400 Hz	200–500 ms	2-15 mA	-	Optimization for specific locations and activities depending on positionality
Nightingale et al.[57] (2019)	eSCS	Medtronic	Paddle	16	Tonic stimulation	T11–L1	Abdominal program: 40 Hz. Cardiovascular program: 35 Hz.	Abdominal program: 420 ms. Cardiovascular program: 300 ms.	Abdominal program: 3.5-6.0 V. Cardiovascular program: 3.5-6.0 V.	Spatially directed differences in stimulation configuration.	-
Terson de Paleville et al.[58] (2019)	eSCS+ locomotor training	Medtronic	Paddle	16	Tonic stimulation	L1–S1	Simulation for standing (10–40 Hz) vs stepping (25–45 Hz)	-	-	-	-
DiMarco et al.[59] (2020)	eSCS	-	Percutaneous	2	Tonic stimulation	T9–T11	50 Hz	0.2 ms	40 V	-	
Gill et al.[79] (2020)	eSCS + body weight supported treadmill training	Medtronic	Paddle	16	Tonic stimulation	T11–L1	20–30 Hz	200–450 μs	2.0–4.1 V	Activity-specific spatially directed stimulation	-

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Table 2. Stimulation parameters of selected studies for epidural spinal cord stimulation facilitation of outcomes following spinal cord injury (continued)

Study	Intervention	Stimulator type	Lead placement	No. of electrodes/lead	Stimulation parameters	Location	Stimulation frequency	Stimulation pulse width	Stimulation amplitude	Stimulation pattern	Stimulation optimization
Gorgey et al.[80] (2020)	eSCS+ exoskeletal-assisted walking training	Medtronic	Paddle	16	Tonic stimulation	T12–S2	40 Hz	-	4–8 V	Spatially selective stimulus	Modified based on patient performance
Peña Pino et al.[81] (2020)	eSCS	Abbott	Paddle	16	Tonic stimulation	T12–L1	-	-	-	Activity-specific spatially directed stimulation based on patient selection of preprogrammed settings	-
Beck et al.[62] (2021)	eSCS+task-specific training	Medtronic	Paddle	16	Tonic stimulation	Lumbosacral	-	-	-	-	Parameters were adjusted to enhance motor performance for standing or stepping
Calvert et al.[63] (2021)	eSCS	Medtronic	Paddle	16	Tonic stimulation	T11–L1	-	-	-	-	Electrode configurations enabled specific motor activation.
DiMarco et al.[83] (2021)	eSCS	-	Percutaneous	2	Tonic stimulation	T9–T11	50 Hz	-	20–30 V	-	-
Herrity et al.[85] (2021)	eSCS+activity-based recovery training	Medtronic	Paddle	16	-	L1–S1	-	-	-	-	-
Ibáñez et al.[64] (2021)	eSCS+activity-based recovery training	Medtronic	Paddle	16	Tonic stimulation	T11–L1	-	-	-	-	Parameters optimized based on individualized maps of motor pools activation
Linde et al.[87] (2021)	eSCS+ locomotor training	Medtronic	Paddle	16	Tonic stimulation	Lumbosacral	-	-	-	-	Stimulation parameters optimized for movement (determined by participants)
Mesbah et al.[65] (2021)	eSCS+ activity-based recovery training	Medtronic	Paddle	16	Tonic stimulation	T12–L2	2 Hz or 30 Hz	450 or 1,000 μs	-	Bipolar electrode stimulation using a single adjacent anode and cathode as well as wide field configurations	Further optimization for individual joint movement.
Squair et al.[66] (2021)	eSCS	Medtronic	Paddle	16	Tonic stimulation	T10–T12	-	-	-	-	Parameters optimized to recruit the lower thoracic spinal segments and increase blood pressure
Smith et al.[88] (2022)	eSCS+activity-based recovery training	Medtronic	Paddle	16	Tonic stimulation	Lumbosacral	-	-	-	-	Stimulation parameter optimized to activate specific motor neuron pools

eSCS, epidural spinal cord stimulation; BWST, body weight supported treadmill training; PWBT, partial body weight bearing treadmill training.

Table 3. Stimulation parameters of selected studies for transcutaneous spinal cord stimulation facilitation of outcomes following spinal cord injury

Study	Intervention	Stimulator type	Stimulation parameters	Location	Stimulation frequency	Stimulation pulse width	Stimulation amplitude	Stimulation pattern	Stimulation optimization
Hofstoetter et al.[30] (2013)	tSCS + treadmill stepping	Schwa-Medico	Tonic stimulation	T11–T12	30 Hz	2-ms width (1 ms per phase)	18 V	Charge-balanced, symmetric, biphasic rectangular pulses	-
Hofstoetter et al.[31] (2014)	tSCS	Schwa-Medico	Tonic stimulation	T11–T12	50 Hz	2 ms	Intensities producing paresthesias but no motor responses in lower limbs	Biphasic pulses for 30 min	-
Bedi et al.[33] (2015)	tSCS + locomotor training	-	Tonic stimulation	T10–L1	Stimulations with carrier frequency of 2.5 kHz modulated to "beat" frequency of 20 Hz	-	Amplitude raised to elicit sensory stimulation	Carrier modulated to "beat" frequency	-
Gerasimenko et al.[34] (2015)	tSCS	NeuroRecovery Technologies Inc.	Tonic stimulation	C5, T11, L1	Carrier frequency of 10 kHz at 5–40 Hz	0.5–1.0 ms	30–200 mA	Biphasic rectangular bursts with carrier frequency administered at beat frequency with spatial specificity for different motor neuron pool activation	-
Hofstoetter et al.[35] (2015)	tSCS + treadmill stepping	Schwa-Medico	Tonic stimulation	T11–T12	30 Hz	1 ms	Target intensities defined as to produce paresthesias covering most of the lower limb dermatome yet subthreshold for leg muscle activation	Charge-balanced, symmetric, biphasic rectangular pulses	-
Bedi et al.[37] (2016)	tSCS	-	Tonic stimulation	T10–L1	Stimulations with carrier frequency of 2.5 kHz modulated to "beat" frequency of 30–90 Hz	-	Raised to elicit sensory stimulation	Carrier modulated to "beat" frequency	-
Minassian et al.[39] (2016)	tSCS + robotic-driven gait orthosis	Schwa-Medico	Tonic stimulation	T11–T12	30 Hz stimulation	1 ms	-	Rectangular, monophasic paired pulses (interstimulus interval 30 ms, 50 ms, 100 ms) or single pulses	-
Gad et al.[40] (2017)	tSCS + exoskeleton + buspirone	-	Tonic stimulation	T11–T12, Co1	30 Hz at T11 and/or 5 Hz at Co1	-	-	-	-

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Table 3. Stimulation parameters of selected studies for transcutaneous spinal cord stimulation facilitation of outcomes following spinal cord injury (continued)

Study	Intervention	Stimulator type	Stimulation parameters	Location	Stimulation frequency	Stimulation pulse width	Stimulation amplitude	Stimulation pattern	Stimulation optimization
Freyvert et al.[69] (2018)	tSCS + buspirone	-	Tonic stimulation	C5	5–30 Hz	-	20–100 mA	-	-
Gad et al.[70] (2018)	tSCS + functional task training	NeuroRecovery Technologies Inc.	Tonic stimulation	C3–C4, C6–C7	30 Hz with carrier frequency of 10 kHz	1 ms	70–210 mA	Carrier modulated to "beat" frequency with biphasic waveform or monophasic waveform	-
Inanici et al.[73] (2018)	tSCS + PT	NeuroRecovery Technologies Inc.	Tonic stimulation	C3–C4, C6–C7	Pulses at frequency of 30 Hz with carrier frequency of 10 kHz	1 ms	80–120 mA	Carrier frequency modulated to "beat" frequency	-
Niu et al.[74] (2018)	tSCS	MagVenture	Tonic stimulation	T11–L3/L4	1 Hz or 30 Hz	250 μs	-	Trains of biphasic single pulse, continuous stimulation for sessions of three periods of 4 min continuous stimulation with a 30s break in between	-
Phillips et al.[50] (2018)	tSCS	ValuTrode	Tonic stimulation	T7–T8	30 Hz	1 ms	10–70 mA	Monophasic pulses for at least 1 min	-
Powell et al.[51] (2018)	tSCS	NeuroConn	Tonic stimulation	T10–T11	-	-	2.5 mA	5 pulses for 20 min with interstimulus interval of 5 sec	-
Rath et al.[52] (2018)	tSCS	ValuTrode	Tonic stimulation	T11–T12, L1–L2	"Beat" frequency of 30 Hz over T11 and 15 Hz during stimulation over L1, with each pulse filled with a carrier frequency of 10 kHz	1 ms	10–150 mA	Monophasic, rectangular pulses with carrier frequency modulated to "beat" frequency	-
Knikou et al.[56] (2019)	tSCS	Digitimer	Tonic stimulation	T10–L1/L2	0.2 Hz	1 ms	Subthreshold and suprathreshold intensities	Monophasic stimuli for 16+ sessions of 60 min	-
Sayenko et al.[77] (2019)	tSCS + locomotor training	ValuTrode	Tonic stimulation	T11–T12, L1–L2	0.2–30 Hz with each pulse filled by a carrier frequency of 10 kHz	1 ms	Up to 150 mA	Monophasic pulses with each pulse filled by a carrier frequency	-
Alam et al.[78] (2020)	tSCS + locomotor training	Digitimer	Tonic stimulation	T11, L1	9.4 kHz burst signal delivered at 0.5–30 Hz	100 μs to 1 ms	Dependent on activity (90–120 mA)	Biphasic stimulation with burst duration at T11 and L1	-

(*Continued*)

Table 3. Stimulation parameters of selected studies for transcutaneous spinal cord stimulation facilitation of outcomes following spinal cord injury (continued)

Study	Intervention	Stimulator type	Stimulation parameters	Location	Stimulation frequency	Stimulation pulse width	Stimulation amplitude	Stimulation pattern	Stimulation optimization
Gad et al.[60] (2020)	tSCS	SpineX	Tonic stimulation	C3–C4, C5–C6, T1–T2	Carrier pulse (10 kHz) combined with a low frequency (30 Hz) burst pulse	1 ms	-	High frequency biphasic carrier pulse combined with a low frequency burst pulse	-
Wiesener et al.[61] (2020)	tSCS + FES + swim training	RehaMove	Tonic stimulation	T11–T12	50 Hz	1 ms	-	Biphasic pulses	-
Wu et al.[82] (2020)	tSCS	Digitimer	Tonic stimulation	T2–T4 (posteriorly), C4–C5 (anteriorly)	0.2 Hz	-	-	Pulses delivered in pseudo-random order or in pairs with 40 ms interstimulus intervals	-
Calvert et al.[63] (2021)	tSCS	Digitimer	Tonic stimulation	T11–L2	0.2 and 2 Hz	1 ms	0–150 mA	Monophasic rectangular pulses	-
Estes et al.[84] (2021)	tSCS + locomotor training	Empi Continuum	Tonic stimulation	T11–T12	50–Hz pulse	-	Highest intensity tolerated by patients or upon reporting paresthesias	Biphasic pulse for 30 min	-
Inanici et al.[86] (2021)	tSCS + functional task training	NeuroRecovery Technologies Inc.	Tonic stimulation	C2+C4 or C4+C6, anterior iliac crests of pelvis	30-Hz base with 10 kHz overlapping frequency	1 ms	0–120 mA	Carrier modulated to "beat" frequency	-

tSCS, transcutaneous spinal cord stimulation; PT, physical therapy; FES, functional electrical stimulation.

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in a study by Estes et al.[84] The most studied American Spinal Cord Injury Association (ASIA) scores were ASIA A (n = 132), followed by ASIA B (n = 67), ASIA C (n = 40), and ASIA D (n = 29).

The main stimulation parameters of the eSCS studies are shown in Table 2. The main stimulation parameters of the tSCS studies are shown in Table 3. Of these studies, 48 used eSCS and 24 used tSCS. Of the studies using eSCS, most studies used a Medtronic stimulator (31 of 48) with 16-electrode paddle leads. The locations of lead placement for both eSCS and tSCS studies are shown in Fig. 2. The highest level of lead placement was C2 via tSCS reported by Inanici et al.[86] The lowest level of lead placement was Co1 via tSCS by Gad et al.[40] The most common and effective level of lead placement for volitional movement of lower extremities was in the range of T10–L2. The most common and effective level of lead placement for volitional movement of upper extremities was in the range of C4–6. For genitourinary function, the most common and effective level of lead placement was L1-S1. Lead placement for pulmonary function studies was most common and most effective at T9–11. The most common level of lead placement for cardiovascular function was T11–L1, which has been shown to be effective in reducing orthostatic hypotension.[40,45,54,57,66,71,72] However, lead placement at T7–8 and L1–S1 were also found to be effective for addressing cardiovascular function.[50,58,76,86] The range of stimulus locations can be seen in Fig. 2. Stimulation parameters varied across the studies. We categorized stimulation parameters into 2 major categories: tonic stimulation, where uniform pulses or pulse trains were fired, or spatiotemporal modulation, where spatially selective stimulation was optimized to induce intended movements. Only one study included spatiotemporal modulation of stimulation, though Rowald et al. (a study published outside of our search parameters) used spatiotemporal modulation as well.[2,15] Pulse widths ranged from 150 μsec to 2 msec. Current intensities ranged from 0.1–15 mA/1–40 V in eSCS studies and

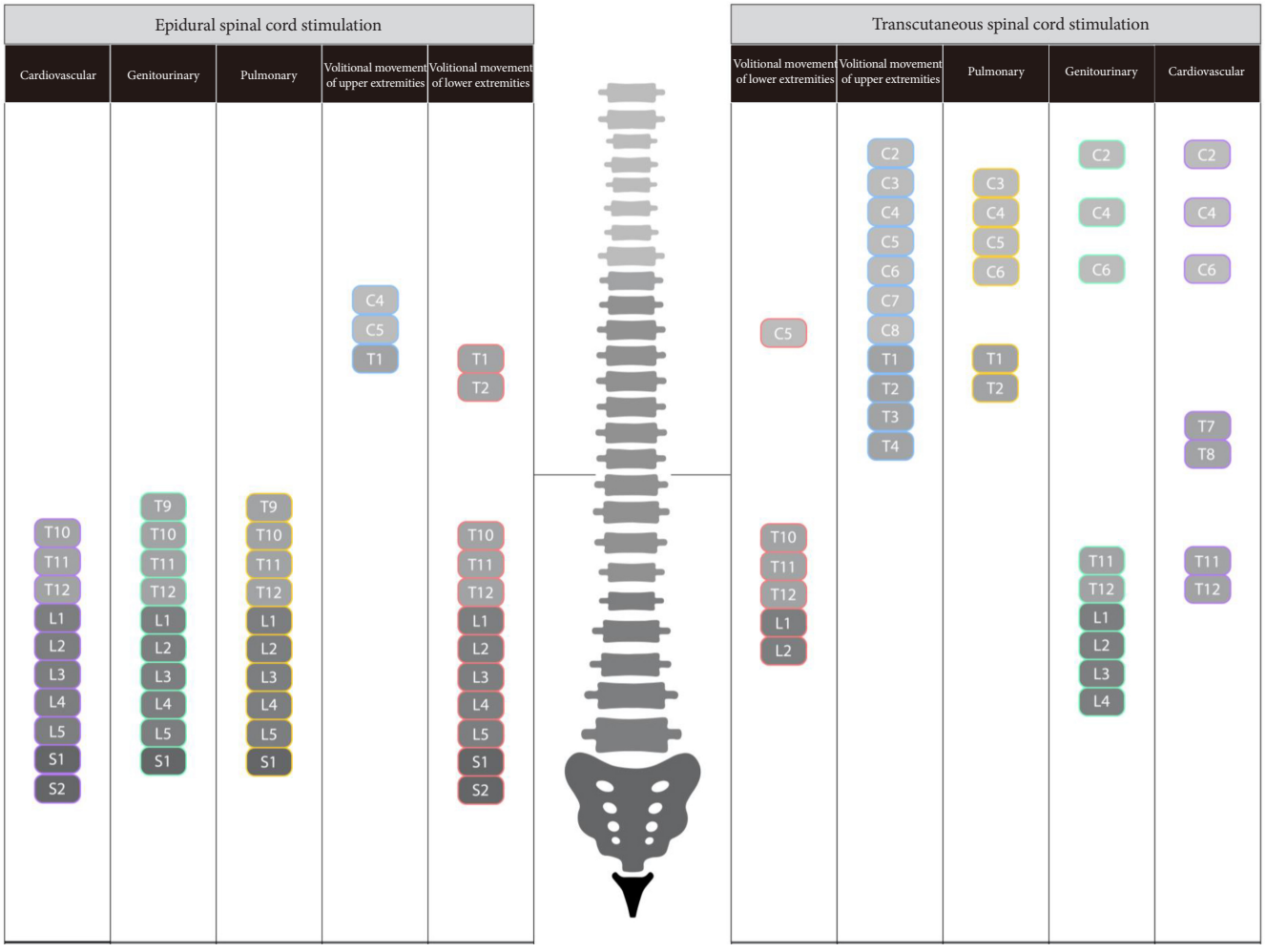

Fig. 2. Range of stimulation locations.

Table 4. Outcomes of selected studies for epidural spinal cord stimulation facilitation of outcomes following spinal cord injury

Study	Intervention	Type of outcome studied	Measured outcome	Complications
Barolat et al.[19] (1986)	eSCS	Volitional: EMG, spasticity	Complete abolition of the spasms, voluntary contraction and relaxation of left quadriceps with eSCS, augmentatory effect on deep tendon reflexes in the lower extremities	None noted
Katz et al.[20] (1991)	eSCS	GU: EMG, bladder volume, peak urinary flow	Postoperative changes in the lower urinary tract function were noted in 6 patients. Urodynamic parameters did not change significantly following implantation in the remaining 17 patients.	-
Herman et al.[21] (2002)	eSCS + BWST therapy	Volitional: gait analysis, whole body metabolic rate, BWS, TSW, OGW, HCA, IWS, sense of effort, spasticity	Immediate improvement in the subject's gait rhythm. After months of training, performance in speed, endurance, and metabolic responses gradually converged with/without eSCS at short distances. Performance with eSCS was superior at long distances.	None noted
Carhart et al.[22] (2004)	eSCS + PWBT therapy	Volitional: EMG, gait analysis, BWS, TSW, IWS, Borg scale for sense of effort	Reduction in sense of effort for over ground walking from 8/10 to 3/10 (Borg scale) and doubled walking speed	Discomfort at 100Hz stimulation
Jilge et al.[23] (2004)	eSCS	Volitional (changes in muscle activity): EMG, induced movement	Enabled initiation and retention of lower-limb extension, elicited posterior root muscle-reflex responses	None noted
Minassian et al.[24] (2004)	eSCS	Volitional (changes in muscle activity): EMG, induced movement	Recruitment of lower-limb muscles in segmental-selective way, characteristic of posterior root stimulation; stimulation at 5–15 and 25–50 Hz elicited sustained tonic and rhythmic activity respectively.	None noted
Ganley et al.[25] (2005)	eSCS + locomotor training	Volitional: EMG, gait analysis, BWS, TSW, OGW, HCA, IWS, sense of effort	Both patients were able to walk faster and further with stimulation than without stimulation.	None noted
DiMarco et al.[26] (2006)	eSCS	Pulmonary: airway pressure, air flow rate, volume of respiratory secretions	Combined T9+L1 stimulation increased airway pressure and expiratory flow rate to 132 cm H_2O and 7.4 L/s respectively	None noted
Huang et al.[27] (2006)	eSCS + partial weight bearing treadmill therapy	Volitional: EMG, gait analysis, BWS, TSW, OGW, IWS, Borg scale for sense of effort	Acute modulations in muscle activities of both patients with stimulation but differences in observed pattern, magnitude, and spectral content of EMGs.	None noted
DiMarco et al.[67,68] (2009)	eSCS	Pulmonary: airway pressure, air flow rate, volume of respiratory secretions	During stimulation, mean maximum airway pressure generation and peak airflow rates 137 ± 30 cm H_2O and 8.6 ± 1.8 L/s respectively.	One nonfunctional lead in each subject, skin breakdown and infection near receiver in one subject, mild leg jerks during SCS (well tolerated), temporary asymptomatic autonomic dysreflexia in three subjects which abated completely with continued SCS
Harkema et al.[28] (2011)	eSCS + stand training	Volitional and GU: EMG, gait analysis, BWS, A/I stand, A/I step, proprioception, bladder storage and voiding	Recovery of supraspinal control of some leg movements only during epidural stimulation 7 months after implantation.	None noted

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Table 4. Outcomes of selected studies for epidural spinal cord stimulation facilitation of outcomes following spinal cord injury (continued)

Study	Intervention	Type of outcome studied	Measured outcome	Complications
Moshonkina et al.[29] (2012)	eSCS + locomotor training	Volitional: EMG, BWS, IWS	Thresholds of muscle responses were significantly lower with bipolar stimulation than the thresholds determined with monopolar stimulation of a single segment.	None noted
Angeli et al.[7] (2014)	eSCS + locomotor training	Volitional: EMG, gait analysis, BWS, TSW, ASIA score	Achieved recovery of intentional movement of legs during epidural stimulation	None noted
Sayenko et al.[32] (2014)	eSCS	Volitional: EMG, BWS	Selective topographical recruitment of proximal and distal leg muscles during rostral and caudal stimulation of lumbar spinal cord	None noted
Rejc et al.[36] (2015)	eSCS + locomotor training	Volitional: EMG, BWS, A/I stand	Achieved full weight-bearing standing with continuous EMG patterns in lower limbs during stimulation	Discomfort (abdominal contractions) caused by stimulation
Lu et al.[38] (2016)	eSCS	Volitional: EMG, handgrip force	Improved hand strength (approximately three-fold) and volitional hand control with stimulation	None noted
Grahn et al.[41] (2017)	eSCS + locomotor training	Volitional: EMG, A/I stand	eSCS with activity-specific training enabled (1) volitional control of task-specific muscle activity, (2) volitional control of rhythmic muscle activity to produce steplike movements while side-lying, and (3) independent standing.	None noted
Rejc et al.[42] (2017a)	eSCS + locomotor training	Volitional: EMG, gait analysis, BWS, A/I stand, STS	Progressive recovery of voluntary leg movement and standing without stimulation, re-emergence of muscle activation patterns sufficient for standing	None noted
Rejc et al.[43] (2017b)	eSCS + locomotor training	Volitional: EMG, gait analysis, BWS, A/I stand, STS	Improved standing (4/4) and stepping (3/4) ability with stimulation and stand/step training.	None noted
Angeli et al.[44] (2018)	eSCS + locomotor training	Volitional: EMG, gait analysis, I. sit, BWS, A/I stand, TSW, OGW, IWS, proprioception	All (4/4) achieved independent standing and trunk stability with stimulation after 287 sessions, some (2/4) achievement of over ground walking with stimulation	One hip fracture during training, one mild drainage from surgery site, one ankle edema
Aslan et al.[45] (2018)	eSCS	Cardiovascular: EMG, plethysmography, BP, BP regulation during orthostasis, HR	In three patients with arterial hypotension, eSCS applied while supine and standing maintained blood pressure at 119/72 ± 7/14 mmHg compared to 70/45 ± 5/7 mmHg without eSCS.	None noted
DiMarco et al.[46] (2018)	eSCS	Pulmonary: airway pressure, air flow rate, volume of respiratory secretions	Paw increased from 20 cm H_2O (8.6% predicted) during spontaneous efforts to 84 cm H_2O at FRC and 103 cm H_2O at TLC during bipolar (T9–T11) SCS and 61 cm H_2O at FRC and 86 cm H_2O at TLC with monopolar (T9) SCS.	Temporary development of asymptomatic autonomic dysreflexia resolving after 5–6 weeks
Formento et al.[47] (2018)	eSCS	Volitional: EMG, gait analysis, proprioception	Continuous eSCS prevented 2/3 participants from detecting leg movements.	None noted
Gill et al.[48] (2018)	eSCS + locomotor training	Volitional: EMG, gait analysis, BWS, A/I stand, TSW, A/I step, OGW, HCA, IWS, spasticity	Achieved independent bilateral stepping with stimulation	None noted

(*Continued*)

Table 4. Outcomes of selected studies for epidural spinal cord stimulation facilitation of outcomes following spinal cord injury (continued)

Study	Intervention	Type of outcome studied	Measured outcome	Complications
Harkema et al.[71] (2018)	eSCS	Cardiovascular: EMG, BP, BP during orthostasis, HR, plethysmography	Persistent hypotension was resolved in four individuals.	None noted
Harkema et al.[72] (2018)	eSCS	Cardiovascular: EMG, BP, BP during orthostasis, HR, plethysmography	Orthostatic hypotension was alleviated in 4 individuals. Improved cardiovascular response was observed after daily eSCS without stimulation.	None noted
Herrity et al.[49] (2018)	eSCS + activity-based recovery training	GU: EMG, storage and voiding, urodynamic parameters via cystometry	All 5 patients showed improvements in bladder emptying.	None noted
Wagner et al.[2] (2018)	eSCS + locomotor training + gravity assist device	Volitional: EMG, gait analysis, EEG, BWS, STS, A/I step, OGW, HCA, IWS, cycling, proprioception, ASIA score	Re-established adaptive control of paralyzed muscles during overground walking stimulation within one week, regained voluntary control over paralyzed muscles without stimulation, regained walking and cycling ability	None noted
Walter et al.[53] (2018)	eSCS	GU: EMG, EKG, external anal sphincter/pelvic floor muscle tone and detrusor pressure, Neurogenic Bowel Dysfunction Score, orgasm	Reduced time needed for bowel management, modulated detrusor pressure and external anal sphincter/pelvic floor muscle tone	None noted
West et al.[54] (2018)	eSCS	Cardiovascular: EMG, plethysmography, BP, BP regulation during orthostasis, cardiac function (contractility, stroke volume, cardiac output), MCA via transcranial doppler	Stimulation resolved the orthostatic hypotension.	None noted
Calvert et al.[75] (2019)	eSCS + locomotor training	Volitional: EMG, induced movement	Enabled intentional control of step-like activity in both subjects within first 5 days of testing	None noted
Cheng et al.[55] (2019)	eSCS + stand training	Volitional: EMG	Spatiotemporal modulation during SCI patient standing leads to activation of an additional neural circuit, which significantly improves patient standing ability.	None noted
Darrow et al.[76] (2019)	eSCS	Volitional, cardiovascular, and GU: EMG, EKG, BP, BP regulation during orthostasis, HR, cardiac function (contractility, stroke volume, cardiac output), MCA, bladder function (storage and voiding, incontinence, synergy), bowel synergy, orgasm	Restoration of cardiovascular function in one patient, achieved orgasm in one patient with and immediately after stimulation, improved bowel-bladder synergy in both patients while restoring volitional urination in one patient	None noted
Nightingale et al.[57] (2019)	eSCS	Cardiovascular and pulmonary: body composition, metabolic rate, oxygen consumption	Increased absolute and relative peak oxygen consumption (15%–26%) during exercise with stimulation; peak oxygen pulse increased with stimulation.	None noted
Terson de Paleville et al.[58] (2019)	eSCS + locomotor training	Cardiovascular and pulmonary: body composition, metabolic rate, oxygen consumption	Increases in lean body mass with decreases on percentage of body fat, particularly android body fat, and android/gynoid ratio from baseline to post training	None noted

(*Continued*)

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Table 4. Outcomes of selected studies for epidural spinal cord stimulation facilitation of outcomes following spinal cord injury (continued)

Study	Intervention	Type of outcome studied	Measured outcome	Complications
DiMarco et al.[59] (2020)	eSCS	Pulmonary: airway pressure, air flow rate, volume of respiratory secretions	Following daily use of SCS, mean inspiratory capacity improved from 1,636 ± 229 to 1,932 ± 239 mL (127% ± 8% of baseline values) after 20 weeks. Mean maximum inspiratory pressure increased from 40 ± 7 to 50 ± 8 cm H_2O (127% ± 6% of baseline values) after 20 weeks.	None noted
Gill et al.[79] (2020)	eSCS + body weight supported treadmill training	Volitional: EMG, gait analysis, BWS, TSW, A/I step, proprioception	During eSCS-enabled BWST stepping, the knee extensors exhibited an increase in motor activation during trials in which stepping was passive compared to active or during trials in which 60% BWS was provided compared to 20% BWS.	None noted
Gorgey et al.[80] (2020)	eSCS + exoskeletal-assisted walking training	Volitional: EMG, A/I stand, A/I step, OGW, IWS	After 24 sessions (12 weeks) of exoskeleton-assisted walking with eSCS, swing assistance decreased from 100% to 35%, accompanied by 573 unassisted steps.	None noted
Peña Pino et al.[81] (2020)	eSCS	Volitional: EMG, cycling, modified Ashworth scale	Some (4/7) achieved volitional movement with no stimulation.	None noted
Beck et al.[62] (2021)	eSCS + task-specific training	GU: EMG, incontinence, storage and voiding, urinary complications, Neurogenic Bladder Symptom Score	In one participant, we observed an increase in episodes of urinary incontinence with worsening bladder compliance and pressures at the end of the study.	None noted
Calvert et al.[63] (2021)	eSCS	Volitional: EMG	eSCS decreased the amplitude of evoked responses of both patients when instructed to perform a full leg flexion	None noted
DiMarco et al.[83] (2021)	eSCS	Pulmonary and GU: airway pressure generation, bowel management, orgasm	Mean pressure during spontaneous efforts was 30 ± 8 cm H_2O. After a period of reconditioning, SCS resulted in pressure of 146 ± 21 cm H_2O.	None noted
Herrity et al.[85] (2021)	eSCS + activity-based recovery training	GU: storage and voiding, urodynamic parameters via cystometry	There was also a significant improvement change in bladder capacity at post-training (70 ± 83 mL, $p < 0.05$) and at follow-up (102 ± 120 mL, $p < 0.05$).	None noted
Ibáñez et al.[64] (2021)	eSCS + activity-based recovery training	Volitional: EMG, A/I stand, STS	Human spinal circuitry receiving eSCS can promote both orderly (according to motor neuron size) and inverse trends of motor neuron recruitment.	None noted
Linde et al.[87] (2021)	eSCS + locomotor training	Volitional: Force sensitive resistors, gait analysis, TSW	Two participants, both with sensorimotor complete SCI graded AIS-A, were able to improve independence of the stance.	None noted
Mesbah et al.[65] (2021)	eSCS + activity-based recovery training	Volitional: EMG	All individuals with chronic and clinically motor complete SCI that participated in the study (n = 20) achieved lower extremity voluntary movements post-eSCS implant and prior to any training.	None noted
Squair et al.[66] (2021)	eSCS	Cardiovascular: plethysmography, BP, BP regulation during orthostasis, HR	eSCS led to real-time hemodynamic stabilization during orthostatic challenges	None noted
Smith et al.[88] (2022)	eSCS + activity-based recovery training	Volitional: EMG, A/I stand, STS	Participants with spared spinal cord tissue (7/11) achieved some knee independence with eSCS	None noted

eSCS, epidural spinal cord stimulation; EMG, electromyogram; BWST, body weight supported treadmill training; BWS, body weight support; TSW, treadmill step/walk; OGW, overground walking; HCA, home and community access; IWS, increased walking speed; PWBT, partial body weight bearing treadmill training; GU, genitourinary; A/I, assisted/independent; STS, sit to stand transition; BP, blood pressure; HR, heart rate; FRC, functional residual capacity; TLC, total lung capacity; SCS, spinal cord stimulation; EKG, electrocardiogram; AIS-A, American Spinal Injury Association Impairment Scale grade A.

Table 5. Outcomes of selected studies for transcutaneous spinal cord stimulation facilitation of outcomes following spinal cord injury

Study	Intervention	Type of outcome studied	Measured outcome	Complications
Hofstoetter et al.[30] (2013)	tSCS + treadmill stepping	Volitional (changes in muscle activity): EMG, gait analysis, treadmill step/walk	Enhanced voluntary lower limb EMG activities in a step-phase appropriate manner with stimulation, modified coordination of hip and knee movements	None noted
Hofstoetter et al.[31] (2014)	tSCS	Volitional (changes in muscle activity): EMG, gait analysis, IWS, spasticity	Increased index of spasticity from pendulum test, increased gait speed during stimulation in two subjects by 39%	None noted
Bedi et al.[33] (2015)	tSCS + locomotor training	Volitional: EMG, ASIA score	Improvement in ASIA score of lower limb by 2 points on right side and by 1 point on left side.	None noted
Gerasimenko et al.[34] (2015)	tSCS	Volitional: EMG	Induced rhythmic leg movements and corresponding coordinated movement EMG activity in leg muscles with stimulation	None noted
Hofstoetter et al.[35] (2015)	tSCS + treadmill stepping	Volitional (changes in muscle activity): EMG, gait analysis, treadmill step/walk	Motor outputs augmentative and step-phase dependent during stimulation, increased hip flexion during swing by 11.3° ± 5.6° across all subjects	None noted
Bedi et al.[37] (2016)	tSCS	Volitional: EMG, ASIA score	Increased firing rate of active muscle units during stimulation	None noted
Minassian et al.[39] (2016)	tSCS + robotic-driven gait orthosis	Volitional (changes in muscle activity): EMG, gait analysis, treadmill step/walk	Increased number of rhythmically responding muscles, augmented thigh muscle activity, and suppressed clonus with stimulation.	None noted
Gad et al.[40] (2017)	tSCS + exoskeleton + buspirone	Volitional and cardiovascular: EMG, gait analysis, BP, HR	Increased patient generation of level of effort, improved coordination patterns of the lower limb muscles, smoother stepping motion, increased blood pressure and heart rate	None noted
Freyvert et al.[69] (2018)	tSCS + buspirone	Volitional: EMG, handgrip strength, ASIA score, spasticity	Increased mean hand strength by 300% with stimulation and buspirone, some functional improvements persisted after interventions discontinued	None noted
Gad et al.[70] (2018)	tSCS + functional task training	Volitional: EMG, handgrip strength	Improved voluntary hand function occurred within a single session in every subject tested.	None noted
Inanici et al.[73] (2018)	tSCS + PT	Volitional: EMG, handgrip force, GRASSP score, ASIA score	Graded Redefined Assessment of Strength, Sensation, and Prehension (GRASSP) test score increased 52 points and upper extremity motor score improved 10 points. Sensation recovered on trunk dermatomes, and overall neurologic level of injury improved from C3 to C4.	Mild, painless hyperemia under electrode, self-resolved
Niu et al.[74] (2018)	tSCS	GU: EMG, storage and voiding	Bladder function improved in all five subjects, but only during and after repeated weekly sessions of 1 Hz TMSCS. All subjects achieved volitional urination.	None noted
Phillips et al.[50] (2018)	tSCS	Cardiovascular: BP, cardiac function (contractility, stroke volume, cardiac output), MCA and PCA velocity	During orthostatic challenge, electrical stimulation completely normalized BP, cardiac contractility, cerebral blood flow, and abrogated all symptoms.	None noted

(*Continued*)

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Table 5. Outcomes of selected studies for transcutaneous spinal cord stimulation facilitation of outcomes following spinal cord injury (continued)

Study	Intervention	Type of outcome studied	Measured outcome	Complications
Powell et al.[51] (2018)	tSCS	Volitional: EMG	No significant differences in change of MEP amplitudes but indication of laterality of response.	None noted
Rath et al.[52] (2018)	tSCS	Volitional: EMG, gait analysis, BWS	During spinal stimulation, the center of pressure displacements decreased to 1.36 ± 0.98 mm compared with 4.74 ± 5.41 mm without stimulation in quiet sitting.	None noted
Knikou et al.[56] (2019)	tSCS	Volitional: EMG	Repeated stimulation increased homosynaptic depression in all SCI subjects. Stimulation decreased the severity of spasms and ankle clonus.	None noted
Sayenko et al.[77] (2019)	tSCS + locomotor training	Volitional: EMG, BWS, A/I stand	All participants could maintain upright standing with stimulation, some (7/15) without external assistance applied to the knees or hips, using their hands for upper body balance as needed.	One case of skin breakage due to electrode defect, resolved after a week without stimulation
Alam et al.[78] (2020)	tSCS + locomotor training	Volitional: EMG, gait analysis, BWS, A/I stand	After 32 training sessions with tSCS, the patient regained significant left-leg volitional movements and improved pinprick sensation.	None noted
Gad et al.[60] (2020)	tSCS	Pulmonary: EMG, airway pressure, air flow rate, volume of respiratory secretions	Improved breathing and coughing ability both during and after stimulation	None noted
Wiesener et al.[61] (2020)	tSCS + FES + swim training	Volitional: EMG, swim analysis, increased swimming speed, cycling, spasticity	tSCS support yielded mean decreases of swimming pool lap times by 19.3% and 20.9% for Subjects A and B, respectively.	None noted
Wu et al.[82] (2020)	tSCS	Volitional: EMG	Resting motor threshold at the abductor pollicis brevis muscle ranged from 5.5 to 51.0 mA. As stimulus intensity increased, response latencies to all muscles decreased.	Asymptomatic sustained 20% or greater change in mean arterial pressure, self-resolved
Calvert et al.[63] (2021)	tSCS	Volitional: EMG	All 4 AIS-B/C participants tested with tSCS demonstrated a reduction in the evoked responses amplitude during stimulation compared to the normalized relaxed value in at least 3 out of 4 of the recorded muscles.	None noted
Estes et al.[84] (2021)	tSCS + locomotor training	Volitional: gait analysis, IWS, spasticity	Significant improvements in walking outcomes following the intervention period	Discomfort, tightness in the abdomen and lower back near electrodes
Inanici et al.[86] (2021)	tSCS + functional task training	Volitional, cardiovascular, and GU: GRASSP, lateral pinch force, spasticity, HR, storage and voiding	Rapid and sustained recovery of hand and arm function. Muscle spasticity reduced and autonomic functions including heart rate, thermoregulation, and bladder function improved.	Mild allergic skin rash

tSCS, epidural spinal cord stimulation; EMG, electromyogram; IWS, increased walking speed; AISA, American Spinal Cord Injury Association; BP, blood pressure; HR, heart rate; GU, genitourinary; PCA, posterior cerebral artery; MCA, middle cerebral artery; BWS, body weight support; A/I, assisted/independent; AIS-B/C, American Spinal Injury Association Impairment Scale grade B/C.

2.5–210 mA/18 V in tSCS studies, though most studies used high intensities close to the subjects' tolerance threshold. The most common and most effective stimulation settings for lower extremity volitional movement were spatially directed based on settings optimized for individual patients performing specific activities (based on muscle group activation). Upper extremity volitional movement was most commonly studied using 0.5–1.0 ms bursts of stimulation at 0.2–90 Hz with carrier frequencies of 2.5–10 kHz, which was found to be effective, though Lu et al.[38] found that spatially directed stimulation optimized for individual patients and activities were also effective. For genitourinary function, the most common stimulation settings were spatially directed and optimized for specific patients and specific activities but optimization for volitional activity of lower extremities was ineffective in improving genitourinary outcomes. Instead, tonic stimulation at 2–60 Hz was effective in improving bladder storage and voiding. Stimulation settings for pulmonary function studies were most common and effective with tonic stimulation at 2–60 Hz. The most common stimulation settings for cardiovascular function were spatially directed, an effective setting for improving cardiovascular outcomes.

The main outcomes of the eSCS studies are shown in Table 4. The main outcomes of the tSCS studies are shown in Table 5. Positive volitional outcomes were measured in terms of electromyography (EMG) activity consistent with activities such as stepping, gait analysis consistent with more fluid movements, increased muscle strength, achievement of independent sitting, increased body weight support, achievement of A/I step, achievement of A/I stand, increased fluidity of sit to stand transition, improved treadmill step/walk, improved overground walking, increased home and community access, increased walking speed, decreased spasticity, decreased sense of effort, or improved ASIA score. Positive genitourinary outcomes were measured in terms of EMG activity consistent with better muscle control, decreased incontinence, increased storage and voiding volume, decreased urinary complications, improved urodynamic parameters via cystometry, decreased time and effort used in bowel management, achievement of orgasm, and decreased Neurogenic Bladder Symptom Score. Positive cardiovascular outcomes were measured in terms of stable blood pressure, improved blood pressure regulation during orthostasis, improved cardiac function, stable heart rate, normal middle cerebral artery blood flow, increased metabolic rate, and increased oxygen consumption. Positive pulmonary outcomes were measured in terms of increased airway pressure, increased ability to cough, increased air flow rate, and decreased volume of respiratory secretions. All but one study reported positive outcomes—Beck et al.[62] reported worsening genitourinary function when using eSCS parameters optimized for volitional movement. Of the 51 studies examining sensorimotor function, 45 studies evaluated lower extremity function and 6 studies evaluated hand function. With regards to autonomic function, 10 studies examined genitourinary function, 8 studies examined pulmonary function, and 11 studies examined cardiovascular function. Four studies reported the return of volitional movement without stimulation.[2,42,78,81] Physical training was described preimplantation in 24 studies and postimplantation in 33 studies, though number of sessions ranged from none to 160 sessions and duration of sessions ranged from 0.5–3 hours. Six studies reported the return of autonomic function during stimulation.[50,59,74,76] One study reported the experience of orgasm for the first time since injury in a patient.[76] Out of 327 patients with varying stimulation and evaluation protocols, 118/127 patients saw improvement in sensorimotor function during stimulation, 51 of 70 patients saw improvement in autonomic genitourinary function during stimulation, 32 of 32 patients saw improvement in autonomic pulmonary function during stimulation, and 32 of 36 patients saw improvement in autonomic cardiovascular function during stimulation. Most patients with improvements in sensorimotor function underwent extensive physical training, ranging from one month to almost 4 years. Of the 127 patients studied for changes in sensorimotor function, 8 patients did not see improvement in motor function, potentially due to lower spasticity scores prior to treatment.[69,81] Seventy-one of 127 patients saw return of volitional movement during stimulation. After months of physical training with adjunctive SCS, 7 of 127 patients saw lasting return of volitional movement in the absence of stimulation for months. In general, there was good tolerability of the intervention by patients with few significant complications.

DISCUSSION

The use of electricity to modulate the nervous system has existed throughout history with variable efficacy. Though use of electricity for neuromodulation has existed since the Ancient Egyptians, studies of electrical stimulation of the spinal cord began in the late 1900s.[89,90] Electrical stimulation of the spinal cord was first tested in 1967 when Norman Shealy applied electrical stimulation subdurally to the dorsal column of cats and found prolonged after-discharge upon electrical stimulation.[90] Based on these findings, Shealy partnered with a graduate engineering student, Thomas Mortimer, to develop an implantable

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spinal cord stimulator by modifying cardiovascular stimulators.[91] Subsequently, use of spinal electrical stimulation was applied in a human patient for temporary severe pain management.[92] More recent approaches to SCS for management of chronic pain include burst stimulation to deliver square waves (5 spikes at 40-Hz bursts with each burst at 500 Hz) or high frequency stimulation (10 kHz) via the Senza system.[93,94] Although the exact mechanism of pain relief during SCS remains unclear, the Gate Control Theory has prevailed as the main explanation for decreased pain perception with stimulation. As hypothesized by the Gate Control Theory, the analgesic effects of SCS are achieved due to greater sensory information being carried by large diameter (touch, vibration, pressure) fibers relative to sensory information being carried by small diameter (pain) fibers to the dorsal horn of the spinal cord.[95] SCS has improved over time, first with the transition of electrode placement from subdural to epidural, then with technological advancements allowing for fully implanted systems with battery-powered pulse generators.[96,97] These advancements have led to further mechanistic rodent studies on the effect of SCS on functional recovery following SCI, such as return of motor, sensory, or autonomic function below the injury site.[16]

The mechanism of action for return of function with SCS after SCI is not fully understood, though current mouse models suggest that SCS transforms dormant tissue to active tissue at the injury site by increasing general excitability.[16] Central pattern generators (CPGs) are dedicated spinal circuits that elicit coordinated rhythmic activity of multiple muscles—CPGs also control reflex influences on alpha motor neurons by facilitating or inhibiting these neurons during specific phases of motion.[98] In rats, stimulation of CPGs in a regular pattern, with the fixed time periods between each stimulation, has been shown to induce adaptive plasticity, promoting spinal cord learning, whereas unsynchronized stimulation has been shown to generate maladaptive spinal plasticity, increasing nociceptive hyperreactivity.[99,100] Coupled with extensive physical training, modulation of excitability allows sensory information to be used as a source of control for voluntary movement through appropriate remodeling of supraspinal and intraspinal pathways in mouse models.[16] However, it should be noted that there are notable anatomical differences between rodents, larger animal models, and humans. For example, rhesus monkeys are more comparable to humans in the projection of the corticospinal tracts. In primates, the corticospinal tract projects through the dorsolateral column, and contains axons originating from both the left and right motor cortex. In contrast, in rodents the corticospinal tract is primarily located in the dorsal column, and these axons exclusively originate from the contralateral motor cortex. A substantial number of corticospinal axons decussate along the spinal cord midline in monkeys, but not in rodents.[101] These anatomical considerations should be taken into account when comparing mechanistic studies with clinical outcomes.

The majority of the functional improvements shown with SCS have been paired with periods of intense motor training. On average, 5.4 months of physical training was required for improvements in volitional movement, such as EMG activity consistent with step-like activity, gait analysis consistent with more fluid movements, increased muscle strength or improved ASIA score—most patients did not completely regain volitional movement. Innovations in approach, such as spatiotemporally modulated dorsal root targeted stimulation, enables activity-based movement within 1 day of stimulation.[15] By pairing stimulation and physical training, plastic changes can be achieved, leading to return of volitional movement in the absence of stimulation. On average, 6.48 months of physical training was required for return of volitional movement in the absence of stimulation in patients—Alam et al.[78] demonstrated the return of volitional movement in the absence of stimulation after 3 months of physical training whereas Rejc et al.[42] demonstrated return of volitional movement in the absence of stimulation after 5.5 years of physical training including 21 months of training prior to stimulator implantation. The remodeling of supraspinal and intraspinal pathways of these patients likely occurs using the same mechanisms underlying learning and memory in the hippocampus—in response to stimulation, AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazoleproprionic acid) and NMDA (N-methyl-D-aspartate) receptors mediate long-term potentiation and long-term depression.[102] Current studies using electricity to treat chronic SCI in rodent models as well as human patients show that electricity is an efficacious neuromodulator for recovery from SCI when paired with physical training, but the optimal amount of training is likely subject dependent and requires further study.

Recently, eSCS and tSCS have both emerged as electricity-based neuromodulation that target the spinal cord, and have shown impressive results in the restoration of function in individuals with SCI. eSCS is defined by the delivery of electricity to the dorsal surface of the dura mater of the spinal cord.[103] Though most commonly used for chronic pain management, eSCS has been shown to improve motor strength and voluntary motor function in patients with SCI.[28,104] tSCS, much like eSCS, elicits spinal cord reflex activity but has electrodes placed on the skin instead of on the dura.[30,105] Through utilizing unique

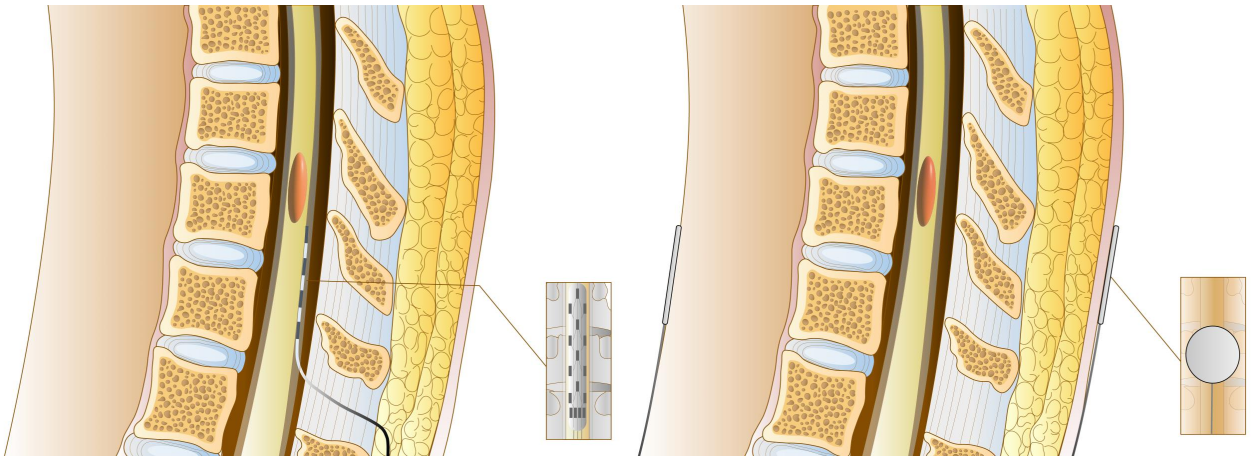

Fig. 3. Epidural (left) and transcutaneous (right) stimulation of the spinal cord. Lesion core is indicated by the orange oval. Epidural spinal cord stimulation electrode arrays are typically placed from T9–L1 or L1–S2. tSCS electrode arrays are typically placed from C2–6 or T11–12. Coronal views of electrodes included. Abdominal cavity not pictured.

waveforms, tSCS permits high-current electrical stimulation to reach spinal networks without causing discomfort.[34] The differences in electrode placement between epidural SCS and tSCS in stimulation location are visualized in Fig. 3. Both techniques activate the dorsal roots, though tSCS stimulation of the skin may contribute to elevated neural activity as well.[73,106] The dorsal roots are comprised of primary afferent fibers—these large diameter proprioceptive sensory fibers have the lowest activation threshold and are preferentially recruited during stimulation.[107] eSCS produces a localized electric field resulting in higher segmental selectivity of the recruited dorsal roots, a feature that allows induction of nonvolitional movements.[24,27] tSCS produces a more distant and unfocused electric field with less segmental selectivity—by providing uniform bilateral coverage of several spinal cord segments, tSCS can increase the general excitability of the spinal cord to induce volitional movement in conjunction with physical training.[35,39,108] Though eSCS and tSCS differ in application, both have been shown to be efficacious in eliciting functional recovery following SCI, and further research should be performed to compare and contrast outcomes with these techniques.

1. Sensorimotor Function

Both eSCS and tSCS have been shown to restore sensorimotor function, most notably measured in return of volitional movement and changes in EMG activity. Of the 127 patients studied for sensorimotor function, 71 patients regained volitional movement during SCS, 51 using eSCS and 20 using tSCS. Of the 51 patients to regain volitional movement during eSCS, 28 patients were noted to have complete SCI (ASIA A) and 23 patients were noted to have incomplete SCI. Of the 20 patients to regain volitional movement during tSCS, none were noted to have complete SCI (ASIA A) and 19 patients were noted to have incomplete SCI, with one patient's SCI injury grade not reported. Usage of eSCS in conjunction with months of physical training induced return of volitional movement without eSCS in 7 patients.[2,42,81] Usage of tonic tSCS at T11 and L1 in conjunction with extensive physical training also induced return of volitional leg movements without stimulation in a single patient, as well as increased pin-point sensation.[78] These studies examine volitional movement, which requires a descending depolarizing input to reach motor threshold, activating motor neurons involved in movement.[109] Immediate improvements in muscle strength and sensation may be explained by modulation of spinal networks into a physiologic state that enables greater access of supraspinal control to sensorimotor networks.[73] In individuals with complete SCI, stimulation is postulated to access local spinal circuitry via dorsal root primary afferent fibers.[107,110] For individuals with an incomplete SCI, SCS is postulated to increase the descending activation of spinal inhibitory circuitry through brainstem-spinal cord loops (orthodromic conduction), as well as activating dorsal column fibers to modulate activity of segmental circuitry involved in regulation of afferent inputs and motor neuron excitability (antidromic conduction).[111,112] The tonic activation of the dorsal root afferent fibers elevates spinal network excitability and brings both interneurons and motor neurons closer to motor threshold, making the circuit more likely to respond to limited post-injury descending drive.[12,113,114] Recent

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preclinical and clinical studies have examined the usage of SCS with targeted spatiotemporal eSCS to activate discrete sensorimotor networks during locomotion and other pattern-based activities.[2,115,116] By developing software to support rapid configuration of stimulation programs that reproduced natural activity-specific activation of motor neurons, Rowald et al.[15] were able to use spatiotemporally modulated eSCS on SCI patients to enable activity-dependent movements such as walking and cycling. Due to the heterogeneity of SCI and differences in spinal anatomy, intensive stimulation optimization or computational modeling for individual subjects may be necessary to increase the efficacy of spatiotemporal stimulation. The studies reviewed show great potential for therapeutic applications of eSCS in restoring motor function in patients with severe SCI, especially with optimized and targeted approaches.

2. Genitourinary Function

Both eSCS at T11–L1 and L1–S2 and tSCS at T11–L3/L4 have been shown to improve bowel-bladder function in patients with SCI. Usage of spatially directed eSCS, specifically on the caudal end of a T11–L1 array or on the rostral end of a L1–S2 array, improved bowel-bladder function.[53,76] Stimulation using the caudal end of a T11–L1 array (pulse width of 390–450 μsec, frequency 25–45 Hz, intensity 4–7 V) in a young male patient (32 years old) 5 years after sustaining motor complete, sensory incomplete SCI increased external anal sphincter/pelvic floor muscle tone and detrusor pressure—these effects significantly expedited bowel management ($p = 0.039$) and decreased the severity of neurogenic bowel dysfunction from severe to minor, as seen in a reduction in neurogenic bowel dysfunction score from 15 to 8 and improvement of general satisfaction scale from 5 to 8.[53] Stimulation using the rostral end of an L1–S2 electrode to excite caudal preganglionic neurons distributed between T1 and L2 in two older female patients in their fifth and sixth decade of life, five and 10 years after sustaining motor and sensory-complete SCI, allowed improvement of bowel-bladder synergy in both patients but recovery of ability to void volitionally but incompletely with residual volumes in only one patients.[76] Conversely, usage of tonic tSCS to stimulate T11–L3/4 at 1Hz improved bladder function during stimulation in 5/5 patients, increasing the volume of urine produced voluntarily from none to 1,120 mL/day, decreasing the frequency of self-catheterization from 6.6/day to 2.4/day, and increasing bladder capacity from 244 mL to 404 mL.[74] SCS is currently hypothesized to enable genitourinary function via an increase in storage and voiding reflexes as well as volitional sphincter control by allowing the micturition circuitry in the sacral cord to appropriately respond to residual descending input from supraspinal micturition centers.[74] Taken together, these studies indicate that SCS of preganglionic neurons near L1 is safe and effective in improving bowel-bladder function in chronic SCI patients.

3. Pulmonary Function

Both eSCS and tSCS have been used to improve pulmonary function in patients with SCI. Regular use of tonic eSCS at T9–L1 (40 V, 30–55 Hz) can lead to pulmonary function changes, notably an increase over 10 and 20 weeks in positive expiratory pressure generation to restore cough.[26,46,59] Additionally, usage of tonic tSCS with a 10-kHz carrier pulse and a 30-Hz burst pulse at the C3–4, C5–6, and T1–12 improved breathing and coughing ability in a patient, with improvements persisting for a few days after tSCS was stopped.[60] Pulmonary function changes in response to SCS are likely due to induction of an excitatory functional state leading to recruitment of respiratory intercostal and trunk muscles.[60] Additionally, dorsal lower thoracic SCS may lead to activation of spinal cord pathways with connections to phrenic motor neuron pools, leading to coactivation of the diaphragm as well.[117] Both eSCS and tSCS hold promise in improving pulmonary function for patients with SCI, though further study of the effects of tSCS are necessary to confirm these findings.

4. Cardiovascular Function

eSCS and tSCS has been demonstrated to restore autonomic cardiovascular function in patients with SCI. Phillips et al.[50] reported return of autonomic cardiovascular function during an orthostatic challenge, noting normalization of blood pressure and heart rate, with tonic monophasic tSCS at 30 Hz at the T7 level. Similar results as discussed with tSCS have been shown with eSCS as well, noting resolution of orthostatic hypotension.[54,118] Cardiovascular function changes in response to SCS, as measured by normalization of heart rate or blood pressure, are likely due to 2 possible mechanisms involving sympathetic preganglionic neuron excitation: (1) small caliber C-fiber afferents excitation, leading to propriospinal interneuron overactivity associated with autonomic dysreflexia, or (2) propriospinal and sympathetic preganglionic neurons excitation, either directly through electrical stimulation or by preferential excitation of large diameter sensory axons that do not elicit autonomic dysreflexia.[50,66] As orthostatic hypotension can have a large negative effect on quality of life, further study of the effects of tSCS and eSCS, on cardiovascular function is necessary.

5. Risk of Bias

A detailed list of risk of bias assessments using ROBINS-I is provided in Supplementary Table 1. Within each study, the risk of bias was judged overall as serious for 66 publications. The bias in measurement of outcomes was the primary source of bias due to lack of blinding in the majority of studies. Additionally, though most studies included patients acting as their own controls with "stimulator on" versus "stimulator off" settings, many patients themselves reported being able to discern between on and off states of the stimulator, and therefore cannot be reliably blinded. The judgement of risk of preintervention domains (confounding, selection, and classification biases) ranged from moderate to serious, where moderate was the lowest possible risk of bias for intervention studies. Most studies were considered low risk for deviation from intended interventions (n = 53) and low risk for missing data (n = 65). Studies ranged from low to moderate with regards to risk of bias for selective reporting.

6. Safety of SCS

SCS is well-documented as a safe treatment for chronic pain due to its reversible and minimally invasive characteristics.[119] Catastrophic complications, such as life-threatening infections or new neurological deficits, are incredibly rare, noting only one reported case of death due to infection and one reported case of paralysis from epidural abscess prior to 2007.[120] The incidence of minor complications with SCS has been reported to be around 30%–40%, though these minor complications occur within 12 months of implantation and are generally resolved.[121] Complications of mechanical origin (rate of 24%–50%), such as lead fracture or disconnection (rate of 5%–9%), lead migration (rate of 0%–27%), or implantable pulse generator failure (rate of 1.7%), are far more common than complications of biological origin (rate of 7.5%), including events like infection (rate of 3%–8%) or dural puncture (rate of 0.3%–2%).[119,122,123] However, the possibility of adverse events in the use of SCS in patients with SCI, particularly with regards to infection, needs further study. Though not present in the studies listed above, there have been a number of patients with surgical site infections after epidural SCS placement.[124] The results of this review indicate that both epidural and transcutaneous SCS are viable options for increasing voluntary motor response of the upper and lower limbs, trunk stability, and autonomic function in patients with SCI. The limited number of complications suggest that both forms of SCS are safe and well tolerated. Both epidural and transcutaneous SCS had cases of dermatologic issues that resolved with time. The 2 reports of potential autonomic dysreflexia self-resolved, one caused by epidural SCS and the other by transcutaneous SCS. Across the studies listed above, there was a 4% complication rate, noting 5 potential cases of autonomic dysreflexia, 3 cases of skin breakage or infection, 1 case of mild drainage from the surgery site, 1 case of a mild skin allergy, 2 cases of a single nonfunctional lead, and 1 case of ankle edema. Stimulation parameters were adjusted to lower levels of patient discomfort, though discomfort at increased frequencies of stimulation (~100 Hz) was more prevalent with epidural SCS.

While research has shown using SCS is a safe and effective option in treating patients with SCI, many steps are necessary for SCS to become a standard treatment for return of motor and autonomic function in SCI patients. The number of clinical trials examining SCS use in SCI has increased over the past 5 years, especially with regards to volitional and nonvolitional movement. A search of ongoing clinical trials pertaining to SCS use in SCI patients was conducted using the publicly available trial registry, ClinicalTrials.gov (https://clinicaltrials.gov/). This search was conducted on March 12th, 2022 and included the search terms "spinal cord injury" and "spinal cord stimulation." After screening for trials specifically using eSCS or tSCS, 60 active trials were identified, with 23 studies using eSCS, 35 studies using tSCS, and 2 studies using eSCS as well as tSCS. 4 studies are currently examining the use of SCS on children with SCI. Forty studies are examining SCS effects on sensorimotor function (both volitional and nonvolitional), 7 studies are examining effects of SCS on autonomic cardiovascular function, 9 studies are examining effects of SCS on pulmonary function, and 9 studies are examining effects of SCS on the genitourinary system. Additionally, 3 studies are examining effects of SCS on muscle electrical activity and 4 studies are examining effects of SCS on muscle spasticity. Additionally, many new clinical trials are studying different stimulation parameters as well as concurrent pharmacologic treatments. To move towards further clinical translation, further clinical trials should adopt more robust research designs to reduce bias, such as including control groups, incorporating randomization before implantation, and adding further blinding to patients and assessors, as well as developing the framework for multicenter studies in an effort to include more patients and make data accessible for external analysis.[125]

The use of SCS to induce functional recovery after SCI is still a fairly new technique—the data gathered across the studies listed in this paper are mostly from case or case-series studies with no appropriate control groups to assess if SCS is a better treatment than placebo or the current standard of care. The patients in the reviewed studies were mostly male (n = 257), indi-

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cating a gender bias—though males are more commonly injured, these results suggest that more females should be included in SCS studies to identify potential gender differences. Additionally, age ranged from 18 to 66 years, but the age recommended for implantation may differ based on the indication for SCS.[126,127] Time between injury and enrollment ranged from 0.1 to 41.1 years, indicating that delayed implantation was not contraindicated. The patients studied had a wide range of injury levels, demonstrating the effectiveness of SCS in treating diverse patient populations, but making it difficult to draw conclusions on the most suitable patient population for SCS. Our review of the literature reveals that further standardization of optimal stimulation frequency and location to elicit specific outcomes, such as bladder control or autonomic cardiovascular response, are necessary. Currently, stimulators used in SCS are designed for chronic pain treatment rather than return of sensorimotor or autonomic function— given that the optimal stimulation parameters differ greatly both between individuals and between specific functions, both sensorimotor and autonomic, stimulators with greater programmability would be greatly beneficial for further studies. Given rat model data has shown that SCS amplifies pre-existing signals in the remaining intact tissue after SCI, individuals with anatomically intact tissue at the injury site may be good candidates for treatment.[4] However, further research needs to be done to assess which subjects will respond most efficaciously to neuromodulation therapy, and whether eSCS or tSCS will be of greatest utility for each individual.

CONCLUSION

The results of this review indicate that epidural and transcutaneous spinal cord stimulation are active areas of study holding promise for improving motor and autonomic function following SCI. Although the results of these studies are positive, significant research still needs to be performed to transition the use of SCS in the restoration of function following SCI from basic research to clinical use. Further mechanistic studies are needed to define optimal stimulation parameters and develop a greater understanding of how SCS interacts with residual connections across the SCI lesion. Based on the current reported results, it is likely that restoration of different functions require optimization by delivering stimulation at distinct spinal levels and with specific parameters. Additionally, structured clinical trials with increased number of subjects need to be performed to evaluate the parameters necessary for greatest efficacy in eSCS and tSCS treatment of patients with chronic SCI.

NOTES

Supplementary Materials: Supplementary Table 1 can be found via https://doi.org/10.14245/ns.2244652.326.

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Supplementary Table 1. ROBINS-I risk of bias analyses of SCS studies

Study	Confounding	Selection	Classification	Deviations from intended interventions	Missing data	Measurement of outcomes	Selection of reported results
Barolat et al.[19] (1986)	Serious	Serious	Serious	Low	Low	Serious	Moderate
Katz et al.[20] (1991)	Serious	Moderate	Moderate	Low	Moderate	Serious	Moderate
Herman et al.[21] (2002)	Serious	Serious	Moderate	Low	Low	Serious	Low
Carhart et al.[22] (2004)	Moderate	Serious	Moderate	Low	Low	Serious	Low
Jilge et al.[23] (2004)	Moderate	No information	Serious	Low	Low	Serious	Low
Minassian et al.[24] (2004)	Moderate	No information	Serious	Low	Low	Serious	Low
Ganley et al.[25] (2005)	Serious	Serious	Moderate	Moderate	Low	Serious	Low
DiMarco et al.[26] (2006)	Serious	Serious	Moderate	Low	Low	Serious	Low
Huang et al.[27] (2006)	Moderate	Serious	Moderate	Low	Low	Serious	Low
DiMarco et al.[67,68] (2009)	Moderate	Moderate	Moderate	Low	Low	Serious	Low
Harkema et al.[28] (2011)	Moderate	Serious	Moderate	Low	Low	Serious	Moderate
Moshonkina et al.[29] (2012)	Serious	Moderate	Serious	Serious	Low	Serious	Moderate
Hofstoetter et al.[30] (2013)	Moderate	Serious	Moderate	Low	Low	Moderate	Moderate
Angeli et al.[7] (2014)	Moderate	Serious	Moderate	Moderate	Low	Serious	Moderate
Hofstoetter et al.[31] (2014)	Moderate	Serious	Moderate	Low	Low	Moderate	Moderate
Sayenko et al.[32] (2014)	Moderate	Serious	Moderate	Low	Low	Serious	Low
Bedi et al.[33] (2015)	Serious	Serious	Serious	Low	Low	Serious	Moderate
Gerasimenko et al.[34] (2015)	Moderate	Serious	Moderate	Low	Low	Serious	Moderate
Hofstoetter et al.[35] (2015)	Moderate	Serious	Moderate	Low	Low	Moderate	Moderate
Rejc et al.[36] (2015)	Serious	Serious	Moderate	Low	Low	Serious	Low
Bedi et al.[37] (2016)	Serious	Serious	Serious	Low	Low	Serious	Moderate
Lu et al.[38] (2016)	Serious	Moderate	Moderate	Low	Low	Serious	Low
Minassian et al.[39] (2016)	Serious	Moderate	Moderate	Low	Low	Serious	Low
Gad et al.[40] (2017)	Serious	Serious	Moderate	Low	Low	Serious	Low
Grahn et al.[41] (2017)	Moderate	Serious	Moderate	Low	Low	Serious	Moderate
Rejc et al.[42] (2017)	Serious	Serious	Moderate	Low	Low	Serious	Moderate
Rejc et al.[43] (2017)	Serious	Moderate	Moderate	Low	Low	Serious	Low
Angeli et al.[44] (2018)	Serious	Moderate	Moderate	Low	Low	Serious	Moderate
Aslan et al.[45] (2018)	Serious	Moderate	Serious	Low	Low	Serious	Low
DiMarco et al.[46] (2018)	Serious	Serious	Moderate	Low	Low	Serious	Low
Formento et al.[47] (2018)	Serious	Moderate	Moderate	Serious	Moderate	Serious	Low
Freyvert et al.[69] (2018)	Serious	Serious	Serious	Moderate	Low	Moderate	Low
Gad et al.[70] (2018)	Moderate	Moderate	Moderate	Moderate	Low	Serious	Low
Gill et al.[48] (2018)	Moderate	Serious	Moderate	Moderate	Low	Serious	Low
Harkema et al.[71] (2018)	Serious	Serious	Serious	Low	Low	Serious	Low
Harkema et al.[72] (2018)	Moderate	Moderate	Moderate	Low	Low	Serious	Low
Herrity et al.[49] (2018)	Serious	Serious	Moderate	Low	Low	Serious	Low
Inanici et al.[73] (2018)	Serious	Serious	Moderate	Low	Low	Serious	Low
Niu et al.[74] (2018)	Moderate	Moderate	Moderate	Low	Low	Serious	Low

(*Continued*)

Supplementary Table 1. ROBINS-I risk of bias analyses of SCS studies (continued)

Study	Confounding	Selection	Classification	Deviations from intended interventions	Missing data	Measurement of outcomes	Selection of reported results
Phillips et al.[50] (2018)	Moderate	Moderate	Moderate	Low	Low	Moderate	Low
Powell et al.[51] (2018)	Serious	Serious	Serious	Serious	Moderate	Serious	Moderate
Rath et al.[52] (2018)	Moderate	Moderate	Moderate	Low	Low	Moderate	Low
Wagner et al.[2] (2018)	Moderate	Moderate	Moderate	Moderate	Low	Serious	Low
Walter et al.[53] (2018)	Moderate	Serious	Moderate	Low	Low	Serious	Low
West et al.[54] (2018)	Serious	Serious	Serious	Low	Low	Serious	Moderate
Calvert et al.[75] (2019)	Moderate	Moderate	Moderate	Moderate	Low	Serious	Low
Cheng et al.[55] (2019)	Serious	Moderate	Moderate	Serious	Low	Serious	Moderate
Darrow et al.[76] (2019)	Serious	Moderate	Moderate	Low	Low	Serious	Low
Knikou et al.[56] (2019)	Moderate	Moderate	Moderate	Low	Low	Moderate	Low
Nightingale et al.[57] (2019)	Serious	Serious	Serious	Low	Low	Moderate	Low
Sayenko et al.[77] (2019)	Moderate	Moderate	Serious	Moderate	Low	Serious	Low
Terson de Paleville et al.[58] (2019)	Moderate	Serious	Serious	Moderate	Low	Serious	Low
Alam et al.[78] (2020)	Serious	Serious	Moderate	Low	Low	Serious	Low
DiMarco et al.[59] (2020)	Moderate	Moderate	Moderate	Low	Low	Serious	Low
Gad et al.[60] (2020)	Serious	Serious	Serious	Low	Low	Serious	Low
Gill et al.[79] (2020)	Serious	Moderate	Moderate	Low	Low	Serious	Low
Gorgey et al.[80] (2020)	Serious	Serious	Serious	Moderate	Moderate	Serious	Moderate
Peña Pino et al.[81] (2020)	Serious	Moderate	Moderate	Low	Low	Serious	Low
Wiesener et al.[61] (2020)	Serious	Serious	Moderate	Low	Low	Serious	Low
Wu et al.[82] (2020)	Moderate	Serious	Serious	Low	Low	Serious	Low
Beck et al.[62] (2021)	Serious	Moderate	Moderate	Moderate	Low	Serious	Moderate
Calvert et al.[63] (2021)	Serious	Moderate	Serious	Low	Low	Serious	Low
DiMarco et al.[83] (2021)	Moderate	Moderate	Moderate	Low	Low	Serious	Low
Estes et al.[84] (2021)	Moderate	Moderate	Moderate	Low	Low	Moderate	Low
Herrity et al.[85] (2021)	Moderate	Serious	Moderate	Serious	Moderate	Serious	Low
Ibáñez et al.[64] (2021)	Serious	Serious	Moderate	Low	Low	Serious	Low
Inanici et al.[86] (2021)	Serious	Serious	Serious	Moderate	Low	Serious	Low
Linde et al.[87] (2021)	Serious	Moderate	Moderate	Low	Low	Serious	Low
Mesbah et al.[65] (2021)	Moderate	Moderate	Moderate	Low	Low	Serious	Low
Squair et al.[66] (2021)	Moderate	Moderate	Moderate	Low	Low	Serious	Low
Smith et al.[88] (2022)	Serious	Moderate	Moderate	Low	Low	Serious	Low

ROBINS-I, Risk of Bias in Non-Randomized Studies of Interventions; SCS, spinal cord stimulation.

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