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Spinal cord stimulation for spinal cord injury – Where do we stand? A narrative review

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ABSTRACT

Recovery of function following a complete spinal cord injury (SCI) or an incomplete SCI where recovery has plateaued still eludes us despite extensive research. Epidural spinal cord stimulation (SCS) was initially used for managing neuropathic pain. It has subsequently demonstrated improvement in motor function in otherwise non-recovering chronic spinal cord injury in animal and human trials. The mechanisms of how it is precisely effective in doing so will need further research, which would help refine the technology for broader application. Transcutaneous spinal cord stimulation (TSCS) is also emerging as a modality to improve the functional outcome in SCI individuals, especially when coupled with appropriate rehabilitation. Apart from motor recovery, ESCS and TSCS have also shown improvement in autonomic, metabolic, genitourinary, and pulmonary function. Since the literature on this is still in its infancy, with no large-scale randomised trials and different studies using different protocols in a wide range of patients, a review of the present literature is imperative to better understand the latest developments in this field. This article examines the existing literature on the use of SCS for SCI individuals with the purpose of enabling functional recovery. It also examines the voids in the present research, thus providing future directions.

1. Introduction

In spite of tremendous progress in modern medicine, spinal cord injury (SCI) can wreck the lives of its victims and their families. It is a catastrophic event that culminates in a deficiency of sensorimotor and/or autonomic functions. Broad classification into complete and incomplete injuries helps in prognosticating the outcome. In addition to the loss of several essential functions, morbidity in patients with SCI can increase due to infections of the lower respiratory or urinary tract, pressure injuries, and deep venous thrombosis. Research so far has helped in improving functional outcomes, limiting complications, and improving quality of life but has not been able to help with motor recovery significantly.[1] Pharmacological agents and stem cell transplantation have shown promising outcomes with regard to neurological recovery in animal models though these interventions were not able to achieve positive results in human studies.[2,3]

In most SCI, there is the presence of intact tissue at the level of injury, which is functionally silent.[4] At the level of SCI lesion, the afferent signals to upper motor neurons are lost. The efferent signals travelling rostrocaudally terminate at the level of SCI lesion. Remnant proprioceptive connections may act as a subsidiary channel for descending signals.[5] Contemporary advances have demonstrated the recovery of coordinated purposeful movements with the aid of extant neural linkages.[6] Of late, there has been increased interest in newer modalities of research, such as Spinal cord Stimulation (SCS). It is majorly divided into Epidural spinal cord stimulation (ESCS) and transcutaneous spinal cord stimulation (TSCS).[7] SCS has been used for the management of pain (failed back syndrome, radicular pain), stable angina, peripheral arterial disease, complex regional pain syndrome, and neuropathic pain.[7] Its use is being explored in Parkinson's disease, spasticity, and SCI rehabilitation.[7–9] SCS has been found to produce rhythmic motor movements in animal models and has gained interest for

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translation into human trials.[10] In this narrative review, we discuss the various human studies conducted on ESCS and TSCS, the present status and the future prospects.

2. Methods

We used the search terms (Spinal Cord Injury OR Spinal Injury OR Tetrapleg* OR Parapleg*) AND (Spinal cord stimulat* OR Epidural Stimulat* OR Transcutaneous Stimulat* OR Neuromodulat*) and conducted a literature search in Medline, Embase and Scopus. Relevant articles in the English language searched for Title/Abstract with available full text (free full text or access available to the authors) were included. Only clinical studies focusing on neurological, autonomic, and functional improvement were included in the review. Studies were included irrespective of the stage of care following SCI. Studies simultaneously involving other interventions or therapies, such as pharmaceuticals, regenerative therapies, and brain stimulation were excluded. Articles discussing sacral neuromodulation and tibial nerve stimulation were excluded. A total of 7124 research studies were identified in the above databases, including 458 Medline, 845 Embase, and 5821 Scopus results. After rejecting duplicates and screening of titles and abstracts, 54 studies were chosen for a detailed reading of the text. After full-text reading, 19 articles were excluded and 14 additional studies were identified through the review of bibliographic references. After screening the articles, a total of 49 articles were included for data extraction and assessment (Fig. 1).

3. Epidural spinal cord Stimulation (ESCS)

ESCS helps deliver stimulation to the spinal cord following a surgical procedure. For ESCS, an array of electrodes are implanted over the dura mater, within a few millimetre distance of the dorsal aspect of the spinal cord. The stimulating interfaces can be placed either percutaneously or by open surgery in which the dura is accessed following the removal of the lamina. Whereas in the former technique, electrode placement is in a single line, in the latter technique, electrodes can be organised in an array of rows and columns on a paddle. The electrodes are linked through lead wires tunnelled under the skin to an often rechargeable programmed rhythm generator that can be surgically placed subcutaneously and its activation can be modulated using a programmer over the skin surface.[11] ESCS for the purpose of motor recovery in SCI usually involves implantation of an array of 12–16 electrodes over the dura mater around L1 to S1 spinal cord level (T10 to L1 vertebral level).

3.1. Evolution of ESCS

Gate control theory, developed in 1959, helped create a new understanding of pain perception mechanisms. It postulates that stimulus to large-diameter fibres (touch, pressure, vibration) suppresses pain signals in small-diameter nerve fibres.[12] This was the scientific basis for the development of the first SCS device in 1968 by Shealy and Mortimer.[2,7] The potential of SCS to improve function in motor impairments was recognised rather unexpectedly. A multiple sclerosis patient with paraparesis, when managed for intractable pain with SCS, surprisingly developed significant improvement in volitional motor power in her legs.[13] The first article on the use of ESCS in SCI individuals was published in 1985.[14] It was discovered by chance quite later that ESCS could help restore voluntary movement in patients with complete SCI.[15,16] Dimitrijevic et al. reported the optimal location of electrodes for reducing spasticity.[16] They found dorsal placement caudal to the site of the lesion as most suitable. They reported rhythmic muscle activity in paralysed legs with tonic ESCS in the supine position in 6 persons with chronic complete SCI. A few of these even exhibited coordinated flexion and extension movements which seemed similar to stepping. These vital observations were one of the earliest hints at the presence of a central pattern generator in human beings for gait.[17] All studies for improvement of function in lower limbs place epidural electrodes at similar levels. Despite these significant effects, the appeal of SCS in motor recovery in SCI waned in the 1990s. Inconsistency mainly was due to a lack of benchmarks that could predict SCS outcomes in patients with differing neurology and lesions along with contention on site of electrode implantations.[11,18] Studies pertaining to motor recovery with ESCS are listed in Table 1.

3.2. Impact of ESCS on lower limb function

The impact of ESCS on the lower limb has been more widely studied as compared to its effect on upper limb function. Herman et al. initially established that epidural stimulators that were being used for pain management could as well be used in individuals with SCI to augment motor recovery and ambulation.[19] In a subject with 3.5 years old C5-6 SCI with AIS −C neurology, they reported with ESCS more effective stepping, less metabolic stress, and the ability to ambulate but with considerable difficulty.[19,20] Harkema et al. (2011) found that a participant with SCI(AIS-B) could achieve full weight-bearing and supraspinal control of a few leg movements with a combination of training and ESCS.[21] They also noted improvement in the bladder along with sexual wellness and temperature regulation after epidural stimulation.[21] Grahn et al. (2017) reported that their participant with SCI (AIS-A) was able to stand, do intentional step-like movements, and later do overground stepping when ESCS was added with task-specific training (multimodal rehabilitation).[22]

Rejc et al. (2017) reported significant improvement in standing ability in four participants (2 AIS-A, 2 AIS-B). The participants had gone through prolonged training in locomotion before the implantation of the epidural stimulator. They hypothesised that standing and stepping were varied functions and would need different programs.[23] Two studies in 2018 were the first to demonstrate independently that AIS A subjects with SCI were able to walk overground with tonic SCS.[24,25] Angeli et al. noted that two out of four AIS B subjects with SCI developed the ability to walk overground after rigorous locomotor training with ESCS and use of assistive devices. The other two participants with complete SCI were able to accomplish stepping partially with body weight support on the treadmill but not overground walking. Voluntary limb movement upon command was observed in the participants only in the presence of ESCS.[25]

SCS has evolved over time. Lead positioning, which was earlier subdural, was shifted to epidural space. Progress in engineering has ushered in the usage of battery-dependent implantable devices.[26] Since the initial applications of SCS were derived from its usage in pain management, the use of tonic SCS was virtually universal until 2018 for motor recovery in individuals with SCI. Formento et al. hypothesised that perpetual stimulation by ESCS would lead to the collision of signals from stimulus to afferent orthodromic impulses, thereby negating each other and rendering tonic SCS ineffective, limiting the utility of applicable stimulation intensities and frequencies of tonic SCS strategies.[10] The firing rates of action potentials in proprioceptive fibres are lower in human beings as compared to rats. In contrast, the transit time is higher. They demonstrated the obliteration of proprioceptive information in humans following antidromic collisions, but similar abolition was not observed in rats.

With this background, Courtine and colleagues developed a new

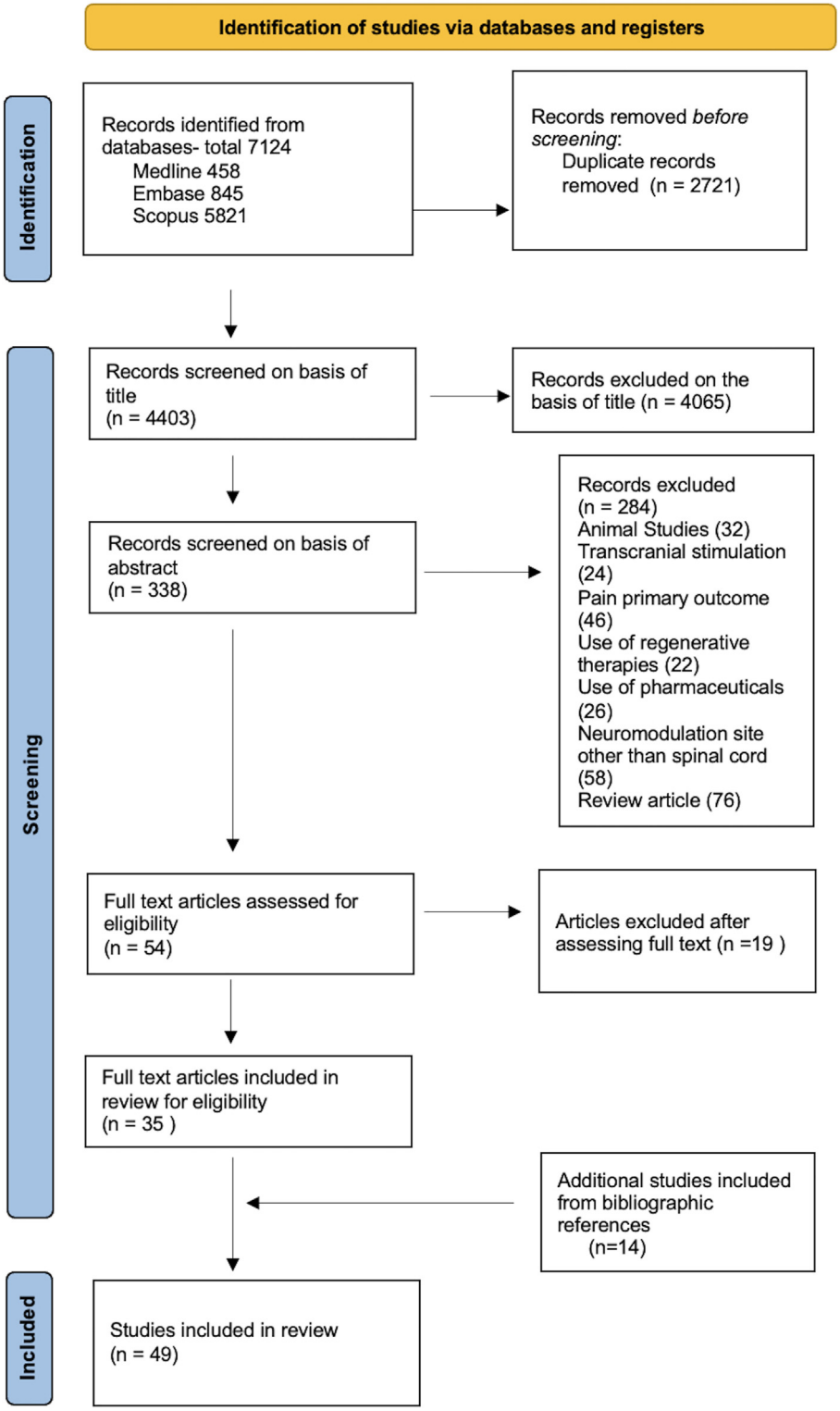

Fig. 1. Prisma Flowchart

approach of spatiotemporal ESCS in pre-clinical studies.[27–29] They conceptualised timely recruitment of proprioceptive circuits in the spinal cord to reproduce natural, task-specific activation of motor neurons.[30] They designed "targeted SCS" or "biomimetic stimulation" to deliver stimulation in a phase-based manner at targeted areas in contrast to continuous nonpatterned stimulation.[31] Use of spatiotemporal ESCS was initially established in rats.[29] The first reported use in human participants was in three cervical incomplete SCI individuals (two AIS-C and one AIS-D) who were wheelchair users for four years and more.[31] A spatiotemporal map of the activity of the motor neuron pool of ambulatory individuals with intact neurology was obtained through Electromyography (EMG)

Table 1
Role of ESCS in motor recovery in persons with SCI.

Role of ESCS in lower limb motor recovery and ambulation in persons with SCI										
S. No.	Study	No. of Subjects	AIS; Neurological level	Place	Primary Outcome	Device	Stimulation site	Stimulation parameters	Intervention and Follow Up	Concurrent Therapy
1	Barolat 1986 19	1	C; C5	Philadelphia, PA, USA	**Motor recovery** Complete abolition of the spasms, voluntary contraction and relaxation of left quadriceps with ESCS, augmentatory effect on deep tendon reflexes in the lower extremities.	Electrode: Filament wire (Clinical Technology Corporation, MO, USA). Stimulator: Not reported	T1 – T2	Frequency: 75 Hz Pulse width: 250 μs Intensity: paresthesia and sub motor threshold	Assessment at 8 and 15 months whilst ongoing ESCS use	None
2	Dimitrijevic et al., 1998 17	6	A; C5-T8	Houston, Texas, USA	**Motor recovery** Rhythmic locomotor-like flexion/extension patterns in the lower limbs	Electrode: Quadripolar 3487A (Medtronic Inc. MN, USA) Simulator: Not reported	T10 – S2	Frequency: 25 –50 Hz Pulse Width: Not reported Intensity: 5 –9 V	Single session of 1 –5 min stimulation	None
3	Herman et al., 2002 20	1	C; C6	Phoenix, AZ, USA	**Ambulation** Immediate improvement in the subject's gait rhythm. After months of training, performance in speed, endurance, and metabolic responses gradually improved, spasticity decreased with/without ESCS at short distances. Performance with ESCS was superior at long distances	Electrode: Pisces-Quadplus (Medtronic Inc. MN, USA) Stimulator: X-TREL (Medtronic Inc. MN, USA)	Lumbar enlargement	Frequency: 20 –60 Hz Pulse width: 800 μs Intensity: sub motor threshold	Single assessment with and without ESCS stimulation	Weight supported treadmill walking
4	Carhart et al., 2004 21	1	C; C5–C6	Phoenix, AZ, USA	**Motor recovery** Reduction in sense of effort for over ground walking from 8/10 to 3/10(Borg scale) and doubled walking speed.	Electrode: Quadripolar 3487A (Medtronic Inc. MN, USA) Stimulator: ITREL 3 Model 7425 (Medtronic Inc. MN, USA)	T10 – L1	Frequency:10 –100 Hz Pulse width: 240–900 μs Intensity: 0.1 –7 V	Up to 2 h/day, with and without ESCS stimulation, 5 sessions/week, 12 months	Weight supported treadmill and over ground walking
5	Minassian et al., 2004 22	10	8A,2B; C4-T10	Vienna, Austria	**Motor recovery** 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.	Electrode: Quadripolar 3487A (Medtronic Inc. MN, USA) Stimulator: ITREL Model 7425 (Medtronic Inc. MN, USA)	T10 – L1	Frequency: 2.2–50 Hz Pulse width: 210 μs Intensity: 1 –10 V	Single assessment whilst ongoing ESCS use	None
6	Ganley et al., 2005 23	2	C; C6-T8	Tempe, AZ, USA	**Ambulation** Both patients were able to walk faster and further with stimulation than without stimulation.	Electrode: Quadripolar 3487A (Medtronic Inc. MN, USA) Stimulator: ITREL 3 Model 7425 (Medtronic Inc. MN, USA)	S1 – S2	Frequency: 20 –60 Hz Pulse width: 800 μs Intensity: Subject 1 sub motor threshold, Subect 2 motor threshold	Single assessment with and without ESCS stimulation	Weight supported treadmill walking
7	Huang et al., 2006 24	2	C; C5-T8	Tempe/ Phoenix, AZ, USA	**Ambulation** Acute modulations in muscle activities of both patients with stimulation but differences in observed pattern, magnitude, and spectral content of EMGs.	Electrode: Quadripolar 3888 (Medtronic Inc. MN, USA)	T10 – L2	Frequency: 20 Hz Pulse width: 800 μs Intensity: 3 –8.5 V	Single assessment with and without ESCS stimulation	Weight supported treadmill walking

Table 1 (*continued*)

Role of ESCS in lower limb motor recovery and ambulation in persons with SCI										
S. No.	Study	No. of Subjects	AIS; Neurological level	Place	Primary Outcome	Device	Stimulation site	Stimulation parameters	Intervention and Follow Up	Concurrent Therapy
						Stimulator: ITREL Model 3470 (Medtronic Inc. MN, USA)				
8	Harkema et al., 2011 25	1	B; C7	Louisville, KY/Los Angeles, CA, USA	**Motor recovery** Recovery of supraspinal control of some leg movements only during epidural stimulation 7 months after implantation.	Electrode: 5-6-5 Specify (Medtronic Inc. MN, USA) Stimulator: Restore ADVANCED (Medtronic Inc. MN, USA)	T11 – L1	Frequency: 5 –40 Hz Pulse width: 210 or 450 μs Intensity: 0.5 –10 V	Prior to ESCS implantation 170 training sessions over 26 months, 29 sessions of on average 54-min stimulation – sessions/ week not reported	Weight supported treadmill walking and parallel bar functional training
9	Angeli et al., 2014 26	4	2A, 2B; C5-T4	Louisville, KY/Los Angeles, CA, USA	**Motor recovery** Achieved recovery of intentional movement of legs during epidural stimulation	Electrode: 5-6-5 Specify (Medtronic Inc. MN, USA) Stimulator: Restore ADVANCED (Medtronic Inc. MN, USA)	T11 – T12	Frequency: 25v or 30 Hz Pulse width: Not reported Intensity: Individualized	~80 training sessions prior to implantation, home based training ~1 h/day, 7 sessions/ week, assessments at 19, 36 & 55 weeks whilst ongoing ESCE use	None
10	Sayenko et al., 2014 27	3	1A, 2B; C7-T4	Louisville, KY/Los Angeles, CA, USA	**Motor evoked responses** Selective topographical recruitment of proximal and distal leg muscles during rostral and caudal stimulation of lumbar spinal cord.	Electrode: 5-6-5 Specify (Medtronic Inc. MN, USA) Stimulator: Restore ADVANCED (Medtronic Inc. MN, USA)	L1 – S2	Frequency: 2 Hz Pulse width: 210 μs Intensity: 0.5 –10 V	Baseline assessment prior to ESCS implantation and 2–3 weeks post whilst ongoing ESCS use	None
11	Rejc et al., 2015 28	4	2A, 2B; C7-T4	Louisville, KY/Los Angeles, CA, USA	**Standing** Achieved full weight-bearing standing with continuous EMG patterns in lower limbs during stimulation.	Electrode: 5-6-5 Specify (Medtronic Inc. MN, USA) Stimulator: Restore ADVANCED (Medtronic Inc. MN, USA)	L1 – S1	Frequency: 25 Hz Pulse width: Not reported Intensity: Sub motor threshold	~80 training sessions prior to implantation, 1 h, 5 sessions/week, 16 weeks (80 sessions) whilst ongoing ESCS use	Parallel bar full weight bearing standing training
12	Grahn et al., 2017 29	1	A; T6	Rochester, MN, USA	**Motor recovery** 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.	Electrode: 5-6-5 Specify (Medtronic Inc. MN, USA) Stimulator: Restore Sensor (Medtronic Inc. MN, USA)	L1 – S1	Frequency: 15, 25 and 40 Hz Pulse width: 210 μs Intensity: Comfort 0 –6 V	27 weeks training prior to implantation, 3 sessions/week, 22 weeks (61 training sessions), whilst ongoing ESCS use	Weight supported treadmill training
13	Rejc et al., 2017 30	1	C7; B	Louisville, KY/Los Angeles, CA, USA	**Motor recovery** Progressive recovery of voluntary leg movement and standing without stimulation, re-emergence of muscle	Electrode: 5-6-5 Specify (Medtronic	T11 – L1	Frequency: 2 Hz Pulse width: Not reported	4 sessions post implantation, pre training, after ~20 weeks training, after ~40 weeks training & ~12 week	Activity based training in lab and home

(*continued on next page*)

Table 1 (*continued*)

Role of ESCS in lower limb motor recovery and ambulation in persons with SCI										
S. No.	Study	No. of Subjects	AIS; Neurological level	Place	Primary Outcome	Device	Stimulation site	Stimulation parameters	Intervention and Follow Up	Concurrent Therapy
					activation patterns sufficient for standing.	Inc. MN, USA) Stimulator: Restore ADVANCED (Medtronic Inc. MN, USA)		Intensity: 0.1 −5 V	follow up with and without ESCS	
14	Rejc et al., 2017 31	4	2A, 2B; C7-T4	Louisville, KY/Los Angeles, CA, USA	**Standing** Improved standing (4/4) and stepping (3/4) ability with stimulation and stand/step training.	Electrode: 5-6-5 Specify (Medtronic Inc. MN, USA) Stimulator: Restore ADVANCED (Medtronic Inc. MN, USA)	L1 − S1	Frequency: 2 and 25 Hz Pulse width: Not reported Intensity: 0.1 −5 V	Assessments (3−14 months apart) over a 4.1-year period pre (21 months) and post ESCS implantation whilst ongoing ESCS use	Full weight bearing standing training
15	Angeli et al., 2018 32	4	2A, 2B; C5-T4	Louisville, KY, USA	**Ambulation** All (4/4) achieved independent standing and trunk stability with stimulation after 287 sessions, some (2/4) achievement of over ground walking with stimulation.	Electrode: Not reported Stimulator: Not reported	L1 − S1 or S2	Frequency: 2 Hz Pulse width: 450 μs Intensity: Individualized	8−9 weeks, 5 days/week training pre ESCS implantation, ~278 sessions (over 85 weeks) and 81 sessions (over 15 weeks) of stimulation and training	Over ground walking training
16	Gill et al., 2020 33	2	A; T3-T6	Rochester, MN, USA	**Motor Recovery (Trunk)** 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	Electrode: 5-6-5 Specify (Medtronic Inc. MN, USA) Stimulator: Not reported	T11 − L1	Frequency: 20 −25 Hz Pulse width: 210 & 450 μs Intensity: 2.0 −7.8 V	6 months training 3 times/week, ESCS placement, 2 × 12 months training periods with a 3-month break, 26 assessments over 34 months − with and without ESCS	Weight supported treadmill training
17	Peña Pino et al., 2020 34	7	6A,1 B; T4-T8	Minneapolis, MN, USA	**Motor function** Some (4/7) achieved volitional movement with no stimulation.	Electrode: Tripole (Abbott, TX, USA) Stimulator: Proclaim Elite (Abbott, TX, USA)	T11 − L1/2	Reported as individualized	14 assessments with and without ESCS over 12 months whilst ongoing ESCS use	None
	Role of ESCS in upper limb motor recovery of patients with SCI									
1	Lu et al., 2016 35	2	B; C5−C6	Los Angeles, CA, USA	**Upper extremity function** Improved hand strength (approximately three-fold) and volitional hand control with stimulation.	Electrode: Artisan (Boston Scientific, CA, USA) Stimulator: Precision Plus (Boston Scientific, CA, USA)	C4 − T1	Frequency: 2 −40 Hz Pulse width: 210 μs Intensity: 0.1 −10 V	Baseline assessments at 1, 2 & 4 months prior to implantation, weekly testing sessions with and without ESCS	Hand and arm activity

Abbreviations: AIS American Spinal Injury Association Impairment Scale; C, Cervical vertebrae; L, Lumbar vertebrae; T, Thoracic vertebrae; S, Sacral vertebrae.

recordings. This included three key areas successively controlling weight bearing, swing, and propulsion. Analogous to pre-clinical studies, ESCS protocols for the SCI participants were exclusively designed to independently aim at dorsal roots innervating respective hot spots.[29] For achievement of desired activity in the open-loop mode, subjects need to coordinate their volitional intent with the predetermined sequence of stimuli. Closed-loop mode used a controller analysing foot trajectory wirelessly in real-time to trigger spatiotemporal stimulation. While being rehabilitated, the three subjects were able to walk better over the ground with ESCS and even without it. Results from the STIMO (Stimulation Movement Overground) clinical trial involving spatiotemporal ESCS with rehabilitation aided by Robot in SCI patients (6 incomplete and 3 complete) revealed the improved ability to walk while supported by a robotic interface.[32] The positive outcomes of the aforementioned research have brought us to the brink of a breakthrough in the rehabilitation of SCI individuals.

3.3. Impact of ESCS on upper extremity motor recovery

The use of ESCS for upper extremity motor recovery is considered even more challenging as compared to the lower limb.[33] Waltz et al., in 1987 reported the use of stimulation of the spinal cord in the cervical region in SCI in 112 patients and reported progress in motor function in 65% of cases though they have not detailed the severity and chronicity of injury.[34]

Lu et al. reported improvement in motor score and improvement in grip strength one week after ESCS in two subjects with cervical SCI (AIS-B). Authors demonstrated improved grip strength even when tested without SCS following repeated stimulation sessions. Both the participants of the study suffered from intractable pain in the shoulder and upper limbs. Results reported for the first participant were from the permanent implant phase, and for the second participant were from a temporary implant phase. Authors theorised that volitional movements were enabled by neuromodulation of the cervical pre-motor group of neurons. EMG findings were also suggestive of the transmission of motor impulses via proprioceptive fibres.[35] Currently, several ongoing pieces of research are targeting upper limb functional improvement, which should be able to guide rehabilitation protocols and lead placement.

3.4. Mechanisms of ESCS for motor recovery

The mechanisms triggering the facilitating effect of ESCS on voluntary movements are not yet precise. The following mechanisms have been proposed.

3.4.1. Recruitment and stimulation of afferent fibres of large-diameter

Computational modelling and electromyography-based studies in SCI subjects support that the SCS triggers larger proprioception fibres. Stimulation generates an afferent signal to the thecal sac that transsynaptically recruits neurocircuits crucial in the management of information from proprioceptive fibres and of motor neuronal activation, mono- and polysynaptic spinal reflex, along with spinal neural networks controlling various components of lower extremity synergistic movements.[11] Lumbosacral nerve roots that are dorsally located have membrane properties favourable for electrical depolarisation. Myelinated axons with large diameters have higher excitability.[36] Differential stimulation owing to axon diameter/fibre size as an isolated hypothesis is insufficient to explain immensely complex motor behavioural consequences of spinal cord stimulation.[2]

3.4.2. Central pattern generators (CPGs)

CPGs are specialised circuitry in the spinal cord that elicit synchronised rhythmic movement of various muscles in the absence of sensory feedback or activation from descending neurons to produce characteristic motor activities in invertebrates and vertebrates such as breathing, chewing, deglutition, crawling, flying, swimming, locomotion and micturition.[37](38) In rats, systematic stimulation of CPGs has been shown to result in adaptive plasticity, promoting spinal cord learning.[39] Neural plastic remodelling in the spinal cord has been extensively researched. ESCS may enable the induction of neuroplasticity in the local region involving afferent fibres, internuncial neurons, and motor neurons.[40] Large-diameter afferent fibres exhibit extensive branching and can thereby modulate multiple locations, including motor agonists and antagonists. They provide inputs to CPGs and may likely influence locomotion. They may also transmit sensory information to supraspinal centres.[41] Most importantly CPGs are instrumental in the generation of movements that may be enabled even without supraspinal signals.[20] Numerous studies are underway to identify CPG neurons consisting of electrophysiological, anatomical, biochemical, genetic, and pharmacological studies.[2,38,42] Research has revealed that CPGs are housed in the anterior aspect of the spinal cord.[43,44] Several animal studies aimed at identifying the CPG interneurons based on the expression of distinctive transcription factors have found specific domains classified into 11 main interneuronal classes (dI1−dI6, V0−V3) in the spinal cord. These neuronal populations exhibit rhythmic activity during locomotion.[45] Reflex pathways formed by interneuronal networks in the spine may be associated with signal transduction. Conspicuous examples have been characterised as intrasegmental, intersegmental, and commissural levels.[46,47] Conventional reflexes consist of Ia- (muscle spindle, myotactic reflex), Ib- (inverse myotatic reflex, Golgi tendon organ), flexor-reflex-afferent (FRA, nocifensive reflex, withdrawal reflex), II-reflex (myotactic polysynaptic).[38] Various muscle groups exhibit differential activation patterns, i.e. monosynaptic pathways activate extensors, whereas indirect polysynaptic reflex pathways activate flexors.[54] These different pathways are probably activated in a phase-based manner.[48,49] Certain attributes of processes involved in weight acceptance, like standing and ambulation, which help to maintain stability in an erect position, are incorporated directly within the motor neuronal networks of the spinal cord.[50] As load bearing increases, extensor tone increases while the tone of flexor muscles diminishes. Coordination of phases of the gait cycle is enabled by real-time integration of the signals from proprioceptive inputs, such as baseline angles of joints and axial loading with spatiotemporal dynamic activation programs.[2,31]

3.4.3. Role of supraspinal pathways

3.4.3.1. Increasing excitability. Evidence supports the involvement of supraspinal centres in influencing function following electrical stimulation. One of the mechanisms of the traumatic spinal lesion is the disruption of connections of efferent tracts results in the loss of signals triggering movement to downstream motor neurons leading to physiological obtundation into a suppressed state that prohibits functional and volitional motor production.[21] Even in several complete SCI patients, some supraspinal connections are preserved.[51] These connections are considered to be inactive functionally.[25] Angeli et al. have observed the influence of audio-visual feedback modulating motor movements and subsequently demonstrated that overground walking with EES was under wilful command.[25,52] Asboth et al., in 2018, in a mouse model of SCI, combined motor cortex stimulation with electrochemical spinal cord stimulation, which restored locomotion and on abandoning motor cortex stimulation, locomotion was disabled.[53] ESCS may increase the net excitability of the spinal cord, thus allowing the attainment of a threshold, enabling functional outcomes, and highlighting the importance of supraspinal pathways. This theory does not explain the persistent long-term functional improvement in SCI patients, even in the absence of spinal cord stimulation, as has been demonstrated in rats as well as human studies.[23,53]

3.4.3.2. Role of the reticulospinal tract. Kathe et al. observed a decrease in metabolic activity in lumbar segments following ESCS and rehabilitation.[32] They identified a group of excitatory lumbar interneurons $SC^{Vsx2:Hoxa10}$ that were especially responsive to ESCS post-SCI and transcriptional activity increased two-fold following ESCS and rehabilitation. These neurons receive input from large-diameter afferents and also connect to the ventral part of the spinal cord. These neurons also receive input from descending reticulospinal tracts which may facilitate supraspinal influence. Asboth et al. emphasised the role of reticulospinal tracts in recovery following spinal cord contusion injury in rats.[53] Despite the

abolition of corticospinal tracts, the voluntary movement was possible following electrochemical stimulation. Along with this, there was the preservation of supraspinal connections through reticulospinal tracts to ventral gigantocellular reticular nuclei. Drug-mediated inhibition of these nuclei resulted in the abolishment of neuromodulation. These findings highlight the role of the reticulospinal tract and $SC^{Vsx2:Hoxa10}$ neurons in long-term functional recovery following neuromodulation. Propriospinal interneurons, which are limited to the spinal cord, have close connections with the reticulospinal tract and can help in relaying descending and ascending signals.[54] Courtine et al., in a study of mice with SCI, demonstrated that propriospinal interneurons facilitated supraspinal control bypassing staggered hemisection at T7 and T12.[5]

3.4.4. Axonal regeneration and upregulation of neurotrophic factors

There is limited evidence to favour that electrical spinal cord stimulation may enhance axonal regeneration across the injury site and further research is required.[55,56] Several studies have demonstrated that following electrical stimulation, there is upregulation of brain-derived neurotrophic factor (BDNF), which is instrumental in promoting neuroplasticity.[57–59] Electrical stimulation may also influence glial cells and modulate inflammation and myelination.[60]

3.5. Issues with ESCS

The electrode array gets engulfed by scar tissue in the epidural space and thus becomes more or less fixed. However, the thecal sac and vertebral column are mobile. Open-loop controllers are not able to execute real-time adjustments to make up for inconsistency in motor recruitment. The absence of integration of reaction from the propriospinal system to the neuroprosthetic controller creates a considerable challenge in the maintenance of balance and stable posture, thus resulting in unsteady and turbulent motion.[2] Closed-loop controllers have the capability to perform integration with feedback signals to implement concurrent stimulus alterations aligned toward the intentional motor output.[31] Volitional control may be enhanced by controlled loop feedback enabled by either physiological activity from the dorsal root ganglion or peripherally implanted sensors.[2,61–63]

Intraoperative imaging with fluoroscopy can guide device implantation by providing gross information about the location. It can be complemented by a neurophysiological assessment during surgery using evoked segmental myotomal monosynaptic EMG-response patterns to direct optimal placement of the array, both in proximal to distal and mediolateral alignment along the neuroaxis.[38] It is yet to be confirmed whether reliable activation of optimal stimulation sites in an awake state is feasible or not. Following implantation, programming of the device has been found to be challenging with multiple trial-and-error evaluations to determine the optimal configuration for stimulation, stimulation parameters, orientations of anode and cathode orientations, exact permutations of pulse frequencies, durations and current. The most efficient configurations of electrodes and settings for stimulators can be different, are individual-specific, and may show task-based variability with time.[21,22,24,25,65–67] A few studies report greater efficiency with phasic stimulation programs in comparison with programs utilising tonic stimulation for motor recovery as they allow synergistic incorporation of necessary proprioception afferent inputs.[10,24,31,66]

4. Transcutaneous spinal cord Stimulation (TSCS)

After its first publication in 2009, TSCS is now being explored more and more in patients with SCI.[68] TSCS is minimally invasive and less costly, being devoid of surgical intervention. Being the most subject-friendly of the current types of SCS, it is under investigation for its impact on rehabilitation and neurological recovery in SCI patients. TSCS involves the placement of electrodes on of skin-surface, as compared to the dura in ESCS, in specific arrangements to generate a flow of current that somewhat crosses the dura stimulating the spinal cord and roots.[69,70] Such currents are permitted by the spine's transversal conductivity but are reduced substantially by the intervertebral discs and ligaments. Manifestation of tingling sensations and activity in muscles in the lower extremities reflects stimulation of deeply placed afferent neural structures in the thecal sac.[49,70,71] By use of distinct waveforms, TSCS allows stimulation with high electric current to access the spinal cord without causing discomfort.[72] Once the skin is stimulated with any of the techniques, it may cause increased neural activity.[73] The primary afferent fibres make up most of the dorsal roots in the spinal cord. These proprioceptive sensory fibres have the minimum activation threshold owing to their larger diameter and are recruited preferentially during stimulation.[74] Studies relevant to motor recovery with TSCS are listed in Table 2.

4.1. Effect on lower extremity function

In most studies, stimulation was given via electrodes over T11-T12 or L1-L2 intervertebral space with anodes over the bilateral iliac crests. Rath et al., in 2018 reported the efficaciousness of TSCS in regaining postural control during sitting following long-standing SCI in 8 (6 AIS-A and 2 AIS-C; injury level C4-T9) participants. EMG revealed increased erector spinae, rectus abdominis, and external oblique activity, thereby helping with stability in the seated position.[75] Sayenko et al., in 2019 reported the use of TSCS in 15 participants (11 AIS-A and 4 incomplete SCI). With stimulation, participants could maintain an upright position without external support (7 of 15 participants) and some with minimal external assistance. No participant could stand with sham stimulation or without stimulation.[76] During TSCS, there was a reduced threshold for motor activation, increased muscle activity in the lower limb observed via surface EMG and increased weight tolerance. Meyer et al., in 2020, demonstrated mildly improved ankle mobility with TSCS in 10 participants with AIS-D neurology.[77] Shapkova et al., in 2020 reported results of exoskeleton-based training with (19 individuals) and without (16 individuals).[78] TSCS was applied at T12 vertebral level. The stimulation magnitude (0.5 ms monophasic square-wave pulses) was around 1.3−1.4 times of threshold of leg muscles as determined by EMG. Participants reported improved coordination, voluntary control, and weight acceptance during stepping. The authors also reported the impact of higher frequencies on improved walking ability with the aid of exoskeleton and spasticity.

Various studies have assessed treadmill-based and over-ground walking with TSCS and reported statistically significant improvements in walking speed, quality and endurance.[79–81] McHugh et al. assessed TSCS with walking-based therapy in a clinical setting in a prospective case series of 10 participants with chronic incomplete SCI.[67] A commercial stimulator was used for stimulation with a biphasic waveform with 1 ms pulses at 50 Hz. The authors concluded that the combined training approach improved walking ability and reported it to be clinically feasible. Estes et al. published results comparing locomotor training combined with TSCS or sham. In participants receiving experimental stimulation, walking speed, as well as the distance, improved.[81]

4.2. Effect on upper limb function

Gad et al., in 2018 assessed EMG recordings and hand grip in 8

Table 2
Use of TSCS in motor recovery in persons with SCI.

Transcutaneous Spinal Cord Stimulation- Motor recovery and ambulation										
S. No.	Study	No. of subjects	AIS; Neurological level	Place	Primary Outcome	Device	Stimulation site/Electrode Placement	Stimulation Parameters	Intervention & Follow Up	Concurrent Therapy
1	Gerasimenko et al., 2015 65	5	NA	St. Petersburg, Russia/Los Angeles, CA, USA	**Motor recovery** Induced rhythmic leg movements and corresponding coordinated movement EMG activity in leg muscles with stimulation	Custom system	Cathodal electrodes paraspinal T11 − T12 or Coccyx 1; Anodal electrodes iliac crests	Pulse mode: Train Frequency: Carrier10 kHz; T11 − T12; 5 Hz Coccyx Pulse width: 1 μs (monophasic) Intensity: 80 −180 mA (induce stepping movement at supramotor and voluntary stepping at submotor threshold)	45-min/stimulation, 1 session/week, 18 weeks (18 sessions)	Passive stepping like motion while in weight supported side laying
2	Hofstoetter et al., 2015 68	3	D; C5-T9	Vienna, Austria	**Ambulation** Motor outputs augmentative and step-phase dependent during stimulation, increased hip flexion during swing by 11.3° ± 5.6° across all subjects	Stimulette r2x+, (Dr. Schuhfried Medizintechnik GmbH, Austria)	Stimulating electrodes paraspinal T11 − T12; Indifferent electrodes paraumbilical level of umbilicus	Pulse mode: Continuous Frequency: 30 Hz Pulse width: 1 μs (biphasic) Intensity: sub motor threshold	Single session, 10 gait cycles	Active treadmill stepping
3	Minassian et al., 2016 69	4	A; C8-T8	Vienna, Austria	**Motor recovery** Increased number of rhythmically responding muscles, augmented thigh muscle activity, and suppressed clonus with stimulation	DS7AH (Digitimer Ltd, England)	T11 − T12	Pulse mode: Continuous Frequency: 30 Hz Pulse width: single, paired, and continuous Intensity:100 −170 mA − motor threshold	Single session with and without momentary stimulation	Weight supported stepping using a robot driven gait orthosis treadmill
4	Powell et al., 2016 70	6	4C, 2D; C6-L1	Louisville, KY, USA	**Motor recovery** No significant differences in change of MEP amplitudes were found between the 3 conditions.	NeuroConn Eldith (Magstim, UK)	Active electrode T10-T11; Reference electrode left deltoid	Frequency: Not reported Pulse mode: Continuous Intensity: 2.5 mA	Intervention consisted of 3 sessions, separated by at least 1 week, in which each subject received the conditions cathodal, anodal, and sham TSCS	None
5	Gad et al., 2017 71	1	A; T9	Los Angeles, CA, USA	**Ambulation** Increased patient generation of level of effort, improved coordination patterns of the lower limb muscles, smoother stepping motion, increased blood pressure and heart rate	Custom system from (Gerasimenko Y. et al., 2015)	Cathodal electrodes paraspinal T11 − T12 or Coccyx 1; Anodal electrodes iliac crests	Pulse mode: Continuous Frequency: Hz T11 − T12; 5 Hz Coccyx Intensity: Optimized efficacy and comfort	7 weeks training, 60-min, 4 weeks baseline training, 1-week TSCS, 1-week pharmacological, 1-week, & 1-week TSCS/ pharmacological	Exoskeleton supported active and passive stepping
6	Powell et al., 2018 72	6	4C, 2D; C6-L1	Louisville, KY, USA	**Motor recovery** No significant differences in change of MEP amplitudes were found between the 3 conditions	NeuroConn Eldith (Magstim, UK)	Cathodal electrodes between T10 − T11; Anodal electrodes deltoid	Pulse mode: Continuous Frequency: Not reported Intensity: 2.5 mA	Intervention consisted of 3 sessions, separated by at least 1 week, in which each subject received the conditions cathodal, anodal, and sham TSCS.	None
7	Rath et al., 2018 73	8	6A, 2C; C4-T9	Los Angeles, CA, USA	**Motor recovery** During TSCS, subjects were able to achieve a more erect posture and	Custom system from (Gerasimenko Y. et al., 2015)	Active electrodes T11 & L1; Reference	Pulse mode: Continuous Frequency: 30 Hz T11;	Single session, with and without stimulation (1−2 min	Postural control

(continued on next page)

Table 2 (*continued*)

Transcutaneous Spinal Cord Stimulation- Motor recovery and ambulation										
S. No.	Study	No. of subjects	AIS; Neurological level	Place	Primary Outcome	Device	Stimulation site/Electrode Placement	Stimulation Parameters	Intervention & Follow Up	Concurrent Therapy
					sustain wider perturbations, as compared to sitting without TSCS.		electrode iliac crests	15 Hz L1; carrier 10 kHz Pulse width: 1 μs Intensity: 10 −150 mA	stimulation per activity)	
8	Sayenko et al., 2019 74	15	11A, 1B, 3C; C4-T12	Los Angeles, CA, USA	**Motor recovery** 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.	Custom system from (Gerasimenko Y. et al., 2015)	Cathodal electrode T11 −12 or L1 − L2; Anodal electrodes illiac crests	Pulse mode: Burst Frequency: T11-30 Hz, L1-15Hz; carrier 10 kHz Pulse width: 1 μs (monophasic) Intensity: up to 150 mA	15 × 120-min stimulation, 3 sessions/ week, 4 weeks (12 sessions)	Standing
9	Meyer et al., 2020 75	10	D; C3-T10	Zurich, Switzerland	**Motor recovery** mmediate significant improvements in ankle motility were observed at 30 Hz, with suppression of pathological activity, assessed by polysynaptic spinal reflex. Non-significant improvements in walking speed were also observed.	Dantec Keypoint Focus Workstation, Natus Medical Incorporated, CA, USA)	Active electrodes T11 − T12; Indifferent electrodes paraumbilical level of umbilicus	Pulse mode: Train Frequency: 15, 30 & 50 Hz Pulse width: 1 μs (monophasic) Intensity: 15 −70 mA, Highest level comfortably tolerated	2 sessions 1−21 days apart, immediate effects of stimulation only	Volitional ankle movement & body weight supported gait activities
10	Shapkova et al., 2020 76	19	12A, 4B, 3C; C5-T12	St Petersburg, Russia.	**Ambulation** Exoskeleton walk training with stimulation improved weight loading capacity and decreased gait asymmetry. Higher frequencies (67 Hz) had an antispasticity effect allowing independent walking. Subjects reported changes in proprioception, sensation, and paresthesias while walking with TSCS.	Viking Select stimulator (USA)	Cathodal electrode T12; Anodal electrodes paraumbilical level of umbilicus	Pulse mode: Not reported Frequency: 1, 3 or 67 Hz Pulse width: 0.5 μs (monophasic) Intensity: 1.3 −1.4 of motor threshold	~45-min stimulation, 3−5 sessions/week, 2 weeks (6−10 sessions)	Exoskeleton walk training
11	Wiesener et al., 2020 77	2	A; T5-T6	Berlin, Germany	**Motor recovery** TSCS support yielded mean decreases of swimming pool lap times by_19.3% and 20.9% for Subjects A and B, respectively.	RehaMove3 (Hasomed GmbH, Germany)	Active electrodes L2 − S2; Indifferent electrode abdomen	Pulse mode: Train Frequency: 50Hz Pulse width: 150−250 or 200−300 μs (biphasic) Intensity: 30 −50 or 40 −60 mA	30−45 min stimulation, 10 weeks (6−7 sessions), 9-month follow up	Swimming
12	McHugh et al., 2020 78	10	4C, 6D; C4-T9	Baltimore, Maryland, USA	**Ambulation** Subjects demonstrated significant improvements in walking speed, endurance, and quality following 8 weeks of training. No subjects reported pain with stimulation. Some subjects reported improvement in bowel, bladder, and pain markers.	Vectra Neo (Chattanooga, TN, USA)	Active electrodes T11 − T12; Indifferent electrodes paraumbilical level of umbilicus	Pulse mode: Continuous Frequency: 50 Hz Pulse width: 1 μs (biphasic) Intensity: 20 −80 mA, sub motor threshold	1-week baseline, 30-min stimulation, 3 sessions/week, 8 weeks (23 sessions)	Gaiting activities
	TSCS- Upper limb function									
1	Gad et al., 2018 79	6	2B, 4C; C4 −C8		**Upper extremity function**	Transcutaneous Electrical Spinal	Cathodal electrode	Pulse mode: Continuous	3 baseline assessments over 10	

Table 2 (*continued*)

Transcutaneous Spinal Cord Stimulation- Motor recovery and ambulation										
S. No.	Study	No. of subjects	AIS; Neurological level	Place	Primary Outcome	Device	Stimulation site/Electrode Placement	Stimulation Parameters	Intervention & Follow Up	Concurrent Therapy
				Los Angeles, CA, USA	Improved voluntary hand function occurred within a single session in every subject tested.	Cord Stimulator (NeuroRecovery Technologies, Inc., CA, USA))	between C3 − C4, C6 − C7; Anodal electrodes iliac crests	Frequency: 30 Hz, carrier 10 kHz Pulse width: 1 μs (biphasic or monophasic) Intensity: 70 −180 mA (maximize handgrip)	days, 60−120 min stimulation, 4 sessions/week (38 sessions)	Functional hand therapy
2	Inanici et al., 2018 66	1	D; C3-4	Seattle, WA, USA	**Upper extremity function** 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.	Transcutaneous Electrical Spinal Cord Stimulator (NeuroRecovery, Technologies Inc., CA, USA)	Cathodal electrodes between C3 − C4, C6 − C7; Anodal electrodes iliac crests	Pulse mode: Continuous Frequency: 30 Hz, carrier 10 kHz z Pulse width: 1 μs (biphasic) Intensity: 80 −120 mA	2 weeks baseline, 90 min sessions, 4−5 days/week, 9 weeks (4 weeks therapy and TSCS, 4 weeks therapy only, 1 week therapy and TSCS), 3 month follow up	Functional upper extremity therapy
3	Inanici et al., 2021 80	6	2B, 2C, 2D; C3−C5	Seattle, WA, USA	**Upper extremity function** Rapid and sustained recovery of hand and arm function. Muscle spasticity reduced and autonomic functions including heart rate, thermo- regulation, and bladder function improved.	Custom device (ONWARD Medical BV, Netherlands)	Cathodal electrodes 1 above and one below level of lesion; Anodal electrodes iliac crests	Pulse mode: Continuous Frequency: 30 Hz, carrier 10 kHz Pulse width: 1 μs (biphasic and monophasic) Intensity: 40 −90 mA, sub motor threshold	4 weekly baseline assessments, 4 weeks task training, up to 120-min stimulation, 3 sessions/week, 4 weeks (12 sessions) 3 months follow up	Functional hand activities
4	Zhang et al., 2020 81	1	A; C5	Newark, NJ, USA	Upper extremity function UE function (GRASSP, NRS, grip strength) improved after 18 sessions of task specific training with TSCS. These gains were maintained without stimulation at 3 months	Transcutaneous Electrical Spinal Cord Stimulator (NeuroRecovery Technologies Inc., CA, USA).	Cathodal electrodes C3 − C4 & C7 − T1; Anodal electrodes iliac crests	Pulse mode: Continuous Frequency: 30 Hz, carrier 10 kHz Pulse width: 1 μs (monophasic) Intensity: 50 and 15 mA	1-week baseline, 60-min stimulation, 2−3 sessions/week, 8 weeks (18 sessions), 3-month follow-up once per month	Functional hand activities

Abbreviations: AIS, American Spinal Injury Association Impairment Scale; C, Cervical vertebrae L, Lumbar vertebrae; T, Thoracic vertebrae; S, Sacral vertebrae.

participants (incomplete SCI) following TSCS.[82] They observed greater grip strength, improved trunk control and hand dexterity. Activation of large interneuronal networks projecting to more distal motor pools was observed in EMG. Inanici et al., in 2018 reported dramatic improvement in upper extremity function in a participant having central cord syndrome (AIS-D) following cervical TSCS and physiotherapy. Upper extremity strength improved to 75% stronger than baseline at 3 months.[73] Zhang et al. reported improvement in Graded Redefined Assessment of Strength, Sensibility, and Prehension (GRASSP) score and hand grip in a participant with chronic complete SCI following 18 TSCS sessions combined with task-specific hand training for 8 weeks.[83]

Inanici et al., in 2021 studied 6 participants with chronic incomplete SCI. TSCS was done by placing one of the electrodes over the cervical disc space level adjacent to the injury level. Anodes are placed over the iliac crest. Primarily upper extremity functions were assessed involving grip along with lateral pinch force, spasticity and neurological recovery. The speed and magnitude of changes were evaluated with and without stimulation. Dexterity and grip strength improved with TSCS. Some cases had benefits on spasticity in the upper extremity.[84]

Huang et. concluded that TSCS combined with task-specific training improves manual dexterity and hand strength in SCI subjects who have a minimum grip strength of more than 0.1 N. As per the results, they hypothesised that some residual hand motor power is essential for improvement after TSCS and rehabilitation.[85]

The main focus of neurophysiological investigations has been on evoked motor potential production and assessment of the characteristics of these reactions as well as elements affecting response modulation. Stimulation is commonly given with paired or singular pulses at low frequencies to assess an evoked response or attain a motor threshold.[86–88] In contrast, therapeutic investigations aim to improve motor responses in SCI individuals by neuromodulation using TSCS. Consequently, TSCS is usually given for extended periods in adjunct to physical therapy. Due to this difference in the targeted outcome, stimulation parameters may vary and may

Table 3
Utility of SCS (Epidural and Transcutaneous) in non-motor functions and spasticity in persons with SCI.

S. No.	Study	No. of Subjects	AIS; Neurological level	Place	Primary Outcome	Device	Stimulation Site	Stimulation parameters	Intervention, Follow Up and outcome	Concurrent Therapy
	ESCS-Genitourinary function									
1	Katz et al., 1991 89	23	A-D; C4-T10	Richmond, VA, USA	Bladder function 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.	Electrode: Resume Model 7492 (Medtronic Inc. MN, USA) Stimulator: Not reported	T1 – tetraplegia T11 – 12 paraplegias	Frequency: 25–130 Hz Pulse Width: 180–450 μs Intensity: 0.25–10.5 V	Baseline assessment prior to ESCS implantation and follow up at 3 months and 1-year whilst ongoing ESCS use	None
2	Herrity AN. et al., 2021 90	10	6A, 4B; C3-T4	Louisville, KY, USA	Bladder function There was also a significant improvement change in bladder capacity (70 ± 83 mL) at post training and follow up 102 ± 120 mL	Electrode: Specify 5-6-5 Medtronic, MN, USA) Stimulator: Restore ADVANCED, Medtronic, MN, USA)	T11 – L1	Frequency: Not reported Pulse Width: Not reported Intensity: Not reported	Single testing session after 160 exercise sessions whilst ongoing ESCS use	Active recovery-based training
	ESCS- Pulmonary function and cough									
1	DiMarco et al., 2020 91	10	NA; C2-T1	Cleveland, OH, USA	Cough Following daily use of SCS, mean inspiratory capacity improved.	Electrode: Not reported Stimulator: Not reported	T9 and T11	Frequency: 50 Hz Pulse width: 200 μs Intensity: 40V	5 testing sessions over 20 weeks whilst ongoing ESCS use	None
2	DiMarco et al., 2006 92	1	C; C5-6	Cleveland, OH, USA	Cough Combined T9+L1 stimulation increased airway pressure and expiratory flow rate to 132 cm H2O and 7.4 L/s respectively.	Electrode: Freehand Epimysial (NeuroControl Corp., OH, USA) Stimulator: Not reported	T9, T11, L1	Frequency: 40–53 Hz Pulse width: 150–200 μs Intensity: 40 V	Single assessment whilst ongoing ESCS use	None
3	DiMarco et al., 2009 93	9	-; C3–C6	Cleveland, OH, USA	Cough During stimulation, mean maximum airway pressure generation and peak airflow rates 137 ± 30 cm H2O and 8.6 ± 1.8 L/s respectively.	Electrode: Not reported Stimulator: Not reported	T9, T11, L1	Frequency: 2–105 Hz Pulse width: 16–800 μs Intensity: 10–40 V	Repeated assessments every 4–5 weeks for 28 weeks, follow up at 3 and then 6-month intervals whilst ongoing ESCE use	None
	TSCS- Pulmonary function and cough									
1	Gad et a., 2020 94	1	A; C5	Los Angeles, CA, USA	Pulmonary function Improved breathing and coughing ability both during and after stimulation	TESCON (SpineX, Inc.)	Cathodal electrodes C5 – C6; Anodal electrodes bilateral shoulders	Pulse mode: Burst Frequency: 30 Hz, carrier 10 kHz Pulse width: 1 μs (biphasic) Intensity: 20 mA	30-min stimulation, session every 2 days minimum, 2 weeks (5 sessions) 1-week baseline, 60 min stimulation 5 sessions/ week, 2 weeks (10 sessions), 1 week follow up	None
	ESCS- Autonomic and Cardiovascular function									
1	Aslan SC. et al., 2018 95	7	4A,3B; C5-T4	Louisville, KY, USA	Autonomic 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.	Electrode: 5-6-5 Specify (Medtronic Inc. MN, USA) Stimulator: RestoreADVANCED (Medtronic Inc. MN, USA)	T11 – L1	Frequency: 2 Hz Pulse width: Not reported Intensity: Maximum tolerated 0–10 V	Single assessment whilst ongoing ESCS use	None
2	West et al., 2018 96	1	B; C5	Vancouver, BC, Canada	Cardiovascular function Stimulation resolved the orthostatic hypotension	Electrode: 5-6-5 Specify (Medtronic Inc. MN, USA) Stimulator: RestoreADVANCED (Medtronic Inc. MN, USA)	T11 – L1	Frequency: 35 Hz Pulse Width: 300 μs Intensity: 3.5 V	Assessment over 2-weeks whilst ongoing ESCS use	None
3		2	A; T4-T8			Electrode:	L1 – S2			None

Table 3 (*continued*)

S. No.	Study	No. of Subjects	AIS; Neurological level	Place	Primary Outcome	Device	Stimulation Site	Stimulation parameters	Intervention, Follow Up and outcome	Concurrent Therapy
	Darrow et al., 2019 97			Minneapolis, MN, USA	Cardiovascular and bowel/bladder function 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 voli-tional urination in one patient.	Three columns[5,6] 16-contact paddle lead (Tripole and Proclaim Elite, Abbott, TX, USA) Stimulator: Primary cell internal pulse generator (Tripole and Proclaim Elite, Abbott, TX, USA)		Frequency: 16–400 Hz Pulse width: 200–500 μs Intensity: 2 –15 mA	Immediate effects of ESCS implantation	
4	Nightingale et al., 2019 98	1	B; C5	Vancouver, BC, Canada	Cardiovascular function Increased absolute and relative peak oxygen consumption (15%–26%) during exercise with stimulation; peak oxygen pulse increased with stimulation.	Electrode: 5-6-5 Specify (Medtonic Inc. MN, USA) Stimulator: RestoreADVANCED (Medtronic Inc. MN, USA)	T11 – L1	Frequency: 35 & 40 Hz Pulse width: 330 & 420 μs Intensity: 3.5 –6 V	6 testing sessions over 3 months whilst ongoing ESCS use	None
	TSCS- Autonomic and cardiovascular function									
1	Phillips et al., 2018 99	5	3A, 2B; C5-T2	Los Angeles, CA, USA	Cardiovascular function During orthostatic challenge, electrical stimulation completely normalized BP, cardiac contractility, cerebral blood flow, and abrogated all symptoms	Not reported	Cathodal electrodes C7 – C8; Anodal electrodes iliac crests	Pulse mode: Continuous Frequency: 30 Hz Pulse width: 1 μs (monphasic) Intensity: 10 –70 mA; normalized blood pressure for at least 1 min	Single session, at least 1-min of stimulation per bout	None
2	Knikou et al., 2019 100	10	2A, 2B, 1C, 5D; C6-T12	New York, NY, USA	Autonomic function Repeated stimulation increased homosynaptic depression in all SCI subjects. Stimulation decreased the severity of spasms and ankle clonus.	DS7A or DS7AH (Digitimer, UK)	Cathodal electrodes T10 to L1 – L2; Anodal electrodes paraumbilical level of umbilicus or iliac crests	Pulse mode: Continuous Frequency: 0.2 Hz Pulse width: 1 μs (monophasic) Intensity: Motor threshold	60-min stimulation, 5 sessions/week,3 weeks (16 sessions)	None
3	Sachdeva et al., 2021 101	1	A; C4	Vancouver, Canada	Autonomic dysreflexia When TSCS was delivered as a multisession therapy for 6 weeks post-SCI, the severity of autonomic dysreflexia was signifi-cantly reduced when tested in the absence of concurrent TSCS	Digitimer DS5, (Digitimer Ltd., UK).	Active electrodes T7 – T8; Reference electrodes iliac crests	Pulse mode: Continuous Frequency: 30 Hz Pulse width: 2 μs (biphasic) Intensity: 20 –30 mA	Stimulation given after 30 s of onset of autonomic dysreflexia, 1 session	None
	TSCS- Spasticity									
1	Hofstoetter et al., 2014 64	3	D; C5-T9	Vienna, Austria	Spasticity Increased index of spasticity from pendulum test, increased gait speed during stimulation in two subjects by 39%	Stimulette r2x+, (Dr. Schuhfried Medizintechnik GmbH, Austria)	Stimulating electrodes paraspinal T11 - T12; Reference electrodes paraumbilical level of umbilicus	Electrodes: Pulse mode: Continuous Frequency: 50Hz Pulse width: 2 μs (biphasic) Intensity: 20 ± 2 V (Supramotor)	30 min stimulation, single session (1 or 2 times)	None
2	Estes et al., 2017 102	18	1B, 6C, 11D; C2-T11	Atlanta, GA, USA	Spasticity Improvement in walking with TSCS. No significant change in spasticity.	Empi Continuum (DJO Global, CA, USA)	Single electrode over T11 – T12; single	Frequency: 50 Hz Pulse mode: Continuous (biphasic)	30-min stimulation, session every 2 days minimum, 2 weeks (5 sessions)	None

(*continued on next page*)

Table 3 (*continued*)

S. No.	Study	No. of Subjects	AIS; Neurological level	Place	Primary Outcome	Device	Stimulation Site	Stimulation parameters	Intervention, Follow Up and outcome	Concurrent Therapy
							electrode over umbilicus	Intensity: Paresthesia in lower legs or feet (sensate) or highest level tolerated (insensate)		

Abbreviations: AIS American Spinal Injury Association Impairment Scale; C, Cervical vertebrae; L, Lumbar vertebrae; T, Thoracic vertebrae; S, Sacral vertebrae.

rationalise the choice of multiple stimulation sites by several therapeutic studies.[89] Although in clinical scenarios, very limited studies demonstrate motor improvement with TSCS, the evidence does favour its practicality and utility, along with it being more consumer-friendly and cost-effective with low risk in comparison to available interventions. Effective TSCS applications generally use moderate frequencies of range 30–50 Hz and long duration pulse of range 0.5 μs–1 ms.[80,81]

5. Utility of spinal cord stimulation (ESCS and TSCS) in non-motor issues faced by SCI patients (relevant studies in Table 3)

5.1. Genitourinary function

Current strategies to manage bladder function in a patient with SCI accompany several side effects. Sacral neuromodulation and percutaneous tibial nerve stimulation (PTNS) relieve symptoms related to bladder overactivity.[90] Though PTNS is non-invasive as compared to sacral neuromodulation, the location of stimulation is distant from the spinal cord and needs multiple sittings and thus having issues with sustainability.[91]

Harkema et. have shown in previous studies that continence, sexual and bowel function in human subjects improve with ESCS.[21] Herrity et al. concluded that ESCS focusing on the parasympathetic outflow to the bladder was adequate to enable efficient micturition. They hypothesised that ESCS influences detrusor contraction strength and external urethral sphincter relaxation.[92] Various trials have reported improvement in bowel and bladder function in SCI patients with ESCS at T11 to L1 and L1 to S2 and TSCS around T11 to L3-L4.[93,94] Darrow et al. reported improvement in bowel and bladder synergy after ESCS in two SCI participants with complete injury. One participant achieved orgasm for the first time since trauma after ESCS. One participant was able to regain volitional urination following ESCS.[93] SCS is currently hypothesised to improve genitourinary function by enabling volitional sphincter control, which is facilitated by access of supraspinal micturition centres to the micturition circuitry in the sacral region. SCS may also help increase storage and voiding reflexes.[95]

Gad et al., in 2018 concluded that TSCS could help normalise the urethral and bladder function in individuals with SCI. They assessed 7 SCI participants and observed increased bladder capacity and enabled voiding, reduced detrusor overactivity and decreased detrusor-sphincter dyssynergia.[96] Kreydin et al. reported in 5 SCI patients (3 AIS-A and 2 AIS-C) decreased detrusor overactivity, improved continence, and enhanced lower urinary tract sensation following TSCS.[97] Niu et al. reported the use of Transcutaneous Magnetic SCS (TMSCS), which is a non-invasive and painless technique for stimulation of the lumbar region of the spine in an attempt to enhance bladder efficiency in five participants with traumatic spinal cord lesion (AIS-A/B).[95] All the participants lacked the ability to self-void. They were given TMSCS every week for 16 weeks. These were followed by sham stimulations given at similar intervals for 6 weeks. Every participant underwent bladder function monitoring. All subjects reported improvement in bladder function while being on TMSCS therapy. All 5 subjects were able to achieve volitional micturition. The urine volume voided voluntarily increased with a decrease in the frequency of self-catheterisation. The bladder capacity increased to 404 mL from 244 mL. So far, the research has supported the role of TMSCS with regard to genitourinary issues only.

5.2. Pulmonary function & cough

SCS has been investigated and found to enhance chest function in individuals with SCI. Sustained use of ESCS around T9 to L1 level (stimulation parameters; 40 V, 30–55 Hz) can allow an increase in positive end-expiratory pressure over 10–20 weeks, thereby helping restore cough.[98–100] The ability to cough is paramount to the prevention of lower respiratory tract infections. It is realised principally by the intercostal muscles and the abdominal muscles (T4-L2).[101] Individuals with injury above T4 develop an ineffective cough, thereby predisposing them to various respiratory infections.[102,103] Spinal cord stimulation at lower thoracic levels (T9-T11) results in triggering of key muscles and restoration of an effective cough.[100] Enhanced cough and breathing were observed in a patient with tonic TSCS (carrier pulse 10-kHz and burst pulse 30-Hz over C3–4, C5–6, and T1–12, with improvements enduring for some days even on discontinuation of TSCS. Recruitment of trunk and intercostal muscles following induction into an excitatory state is considered to facilitate improvement in lung function.[104]

5.3. Autonomic & metabolic issues in SCI

Autonomic dysfunction increases morbidity in SCI individuals.[105] They are prone to develop metabolic issues, coronary artery disease, type 2 diabetes and obesity. This is in part due to decreased potential for mobility as well as deranged autonomic reflexes to exercise in cervical SCI. Sympathetic activation which helps elevate blood pressure (BP), heart rate (HR), mediate sweating response, and appropriate substrate breakdown, is inappropriate in individuals with cervical SCI.[105] In athletes with traumatic spinal cord lesions rostral to T1, the catecholamine levels are very low.[106] A low cervical injury is not significantly different from a high thoracic injury (i.e., T4) from a motor control standpoint. Injury at C8 is differentiated from T4 by the autonomic response to exercise.[105] ESCS and TSCS have been reported to have a positive impact on autonomic functions though how this is made possible remains to be elucidated.[105,107]

5.3.1. Effect of SCS on blood pressure

In those with orthostatic intolerance, blood pressure can be

increased by triggering at several sites (e.g., T6 or T11 to L1) and with various frequencies (e.g., 30 vs 120 Hz).[108] Stimulation of peripheral nerve, either in the presence or absence of contraction in muscles can also raise BP by 10–30 mmHg, comparable to that seen with TSCS or ESCS.[108] Rise in BP is mediated by the constriction of vessels in the splanchnic region. This is mediated by sympathetic activation from T6-T12. Therefore it is pretty surprising that even stimulus given at caudal levels (L1-S1) attains adequate blood pressure in spite of a lack of lower limb muscle activity. These observations support the presence of internal spinal links ascending to thoracic spinal preganglionic circuits.[105] Individuals with traumatic spinal lesions at or below T6 and complete motor weakness maintain autonomic responses comparable to normal subjects.[109]

5.3.2. Effects of SCS on metabolism

Several isolated reports suggest that SCS can improve autonomic nervous system control of sweat gland activity in chronic SCI. An appropriate assessment is needed to define the role of SCS and its outcome in this regard. The adrenal gland is innervated by T6 to T10 spinal segments. Cervical-level SCI individuals have low catecholamine and free fatty acid (FFA) levels.[110–112] The above factors add up to reducing resting and activity-associated energy consumption in these subsets of SCI. Even vigorous exercise will burn calories similar to a sedentary state in comparison with neurologically intact controls.[113] SCS enhanced FFA breakdown as opposed to glucose. It is associated with improvement in maximal exercise response and endurance.[106,114]

5.3.3. Mechanisms influencing autonomic & metabolic system via SCS

SCS at lumbar levels is known to improve blood pressure in orthostatic intolerance via splanchnic vasoconstriction, which derives its nerve supply from T6-T12. Mechanisms influencing metabolism at the spinal level would likely involve the triggering of ascending tracts and their linkages with thoracic sympathetic circuits.[105] SCS at a similar spinal location with the same parameters of stimulation can result in a contradictory impact on BP. Transcutaneous stimulation at T7 or T8 diminished the increase in BP provoked by stimulus in the rectum, whereas transcutaneous stimulation at T7 or T8 raised BP in response to orthostatic hypotension.[115,116] Sachdeva et al. theorised that irritable triggers such as digital stimulus were suppressed by spinal cord stimulation that recruited large diameter fibres.[116] All studies reported the use of pulsed stimulation except Shelyakin et al.,[117] who stimulated using direct current and reported a surge in HR of subjects along with improved lower extremity movements that they ascribed to thoracic paravertebral ganglia activation. Retrograde labelling using injectable pseudorabies virus (PRV) and electrophysiological assessments have consistently shown descending signals to spinal neurons innervating adrenal, heart, blood vessels, temperature regulation, adipose and skeletal muscle tissues. In this framework triggering of locomotion occurs in tandem with a surge in sympathetic activity to metabolic and homeostatic systems.[118] This helps explain the improvement in sympathetic functions when SCS is used for the activation of lower limb motor abilities.

An increase in fatty acid metabolism following upper lumbar SCS is attributed to adrenergic targets to white adipose tissue. It results in higher endurance and fatty acid utilisation as opposed to glucose oxidation.[106,114] Activation of proprioceptive afferents may lead to increased activation of spinal preganglionic neurons via interneurons innervating the cardiovascular, metabolic and sudomotor tissues at various spinal levels.[119] These findings support the application of neuromodulation strategies targeting the autonomic system for homeostasis under various stresses and enhanced exercise tolerance, thereby avert or defer vascular and metabolic diseases frequently observed in chronic SCI.

5.4. Neuropathic pain in SCI patients

SCI has several disturbing consequences, including among them high rates of chronic pain and altered sensory function. According to some estimates, 30%–80% of SCI patients suffer from long-standing pain that develops after an injury.[120] The neuropathic pain is often described as shooting, stabbing, sharp or burning pain. It occurs in a dermatomal distribution and is, at times, intractable in spite of extensive medicinal intake.[121] Severe pain distributed at the neurological level of injury or adjacent to it is frequently seen in SCI patients.[122] Conventional SCS may suppress pain by acting at the spinal or peripheral level. Relief in neuropathic pain in SCI patients has been observed to be less with conventional SCS when compared to those patients with pain due to failed back syndrome or peripheral neuropathic origin. Several studies and a review in 2009 have reported that conventional SCS has unsatisfactory results with only a 30–40% success rate. As of now, the evidence does not support SCS use for neuropathic pain.[123]

6. Technical parameters in SCS

6.1. Lead placement

Leads have been placed in various combinations for TSCS, with the highest at C2 and the lowest at Co1.[84,104] For voluntary muscle activity in the lower extremities, the most frequent and efficient placement of leads was in the range of T10-L2. For voluntary muscle activity in the upper limbs, the most frequent and efficient level for placement of leads ranged from C4–6. Placement of leads at T11 to L1 has proven efficacious in decreasing orthostatic hypotension.[104,124–127] Although for effectively managing cardiovascular function, placement of leads at L1-S1 and T7–8 was also effective. The most frequent and efficient placement of leads for bladder function was L1-S1. In most studies assessing pulmonary function, leads were placed at T9-11.[64,84,115,128]

6.2. Stimulation parameters

Stimulation parameters can be divided into 2 types: tonic stimulation involving the firing of uniform pulses or spatiotemporal modulation, wherein targeted stimulation is optimized to produce intended movements. Most studies have used tonic stimulation.[31,129] Pulse widths were in the range of 150 microsec to 2 msec. Current intensities were in the range of 0.1–15 mA/1 to 40 V in studies on ESCS. In studies on TSCS, current intensities were in the range of 2.5–210 mA/18 V, although many studies used higher intensities almost up to the participant's tolerance threshold.

Stimulation to induce voluntary activity in lower limbs was not efficacious in enhancing bladder function. In order to improve voiding and bladder storage, tonic stimulation ranging from 2 to 60 Hz was found to be effective. For pulmonary functions as well, tonic stimulation at 2–60 Hz was effective. Most studies on TSCS used a continuous pulse mode, with the rest of them using train/burst modes. While some had used an alternating or biphasic waveform, others used a direct current or monophasic waveform. There was an absence of consistency across studies with respect to the specificity of stimulation parameters used for certain outcomes.[130] In humans, continuous ESCS fails to facilitate meaningful locomotion without rehabilitation. This is hypothesised due to the cancellation of proprioception feedback. Burst stimulations and Spatiotemporal stimulations mitigate this issue. Spatial and temporal adjustment of the amplitude and frequency according to the profile of the proprioceptive feedback would facilitate the

modulating activity of motor neurons. Using Computational modelling, Formento et al. concluded that high frequency and low amplitude (5 pulses at 600 Hz) ESCS would prevent the cancellation of proprioceptive feedback at the same time allowing the activation of motor neurons.[10] Several scores and formulas are hypothesised to be helpful in delineating patient-specific stimulation profiles. Further research will help broaden the role of spatiotemporal stimulation.[131]

7. ESCS vs TSCS

Both techniques have basic differences in methodology that have an impact on the respective areas of application and efficacy. ESCS, placed over dura mater, yields a focused electric field leading to greater segmental selectivity in recruiting posterior roots, a characteristic that allows the generation of nonvolitional movements.[48,70,132] TSCS, acting via skin surface electrodes, creates a more far-off and diffuse electric field, albeit with reduced segmental selectivity. By uniformly stimulating a number of segments of the spinal cord, TSCS increases the global sensitivity of the spinal cord to effect voluntary movement when combined with physiotherapy.[133,134] Different electrode models and their selective placement may permit some rostrocaudal discrimination,[135] while the side-to-side selectivity of dorsal root stimulation is yet to be proved. Moreover, because it involves the usage of skin surface electrodes besides variation in stimulation conditions depending on body position, TSCS cannot be applied chronically.[136] ESCS hence seems to be a convincing method to increase or prompt, purposeful motion after SCI, which may lead to better outcomes in gait therapy.[29] Being simple and non-invasive, TSCS may be beneficial in issues where uniform spinal cord segment stimulation is helpful such as lower limb spasticity, or to enhance outcomes of various locomotor therapies.[71,137]

8. Adverse events

Sivaganesan et al. analysed retrospectively and found a 13% complication rate with SCS. Spinal cord stimulators are considered amongst frontrunners of injury among all used medical devices following hip prostheses and implantable insulin pumps.[138] An economic analysis performed by the United Kingdom's National Institute of Health and Clinical Excellence assessing the application of SCS for neuropathic pain management has shown the treatment to be cost-effective.[139] Though similar studies assessing the cost-benefit ratio of SCS in neurological recovery in SCI individuals are not available.

The need for the removal of epidural electrodes is not uncommon, which is a challenging surgical procedure as, with time, electrodes get encapsulated in epidural fibrosis.[140]

Infection is the most common complication, with incidence up to 5%. It may be managed by antibiotics and require even removal of the device and reimplantation following healing from sepsis.[141] Rate of infection is higher than other implantable electronic devices, for instance, cardiac pacemakers (infection rate 0.5–2.2%).[142]

Lead migration incidence, which earlier used to be very high (13–22%), has gone down (1.4–2.1%) as techniques of implantation have evolved.[143,144] If the lead migrates, it may need relocation or substitution of the electrode surgically. Reported adverse events of TSCS to include pain or discomfort following stimulation of nociceptive receptors in the skin, increased spasticity seen in one participant, initial intolerance of the procedure, and skin fissuring due to the concentration of current under the electrodes. TSCS may induce autonomic dysreflexia in SCI individuals, and therefore its translation in home-based programs will need caution.[130,145]

9. SCS-where do we stand and what are future prospects?

The demographic distribution and SCI characteristics of the population with SCI represented by the studies included match that of the general populace, with the majority being incomplete injuries and male participants. Multicentre trials are potent ways to increase the sample size for relatively rare health conditions such as SCI since most studies had less than 10 participants.

To deal with the diverseness of SCI, it is essential for upcoming research to sort and classify SCI subjects by their injury grade and level to inform treatment protocols better. Furthermore, the inclusion of other markers relevant to spinal cord injuries, such as radiology and other clinical assessments, may better classify participants to appreciate possible differences in outcomes of SCS. Recovery outcomes following SCS are directly linked to the severity of the lesion. Many studies have mentioned the neurology as motor incomplete or complete and proper subgrouping according to the AIS classification will shed more light on the effectiveness of SCS in complete SCI. Anatomical and physiological proof of remnant descending white matter and voluntary signals have been realised in an increasing number of AIS A subjects.[146,147] McKay et al. analysed 41 patients with AIS-A neurology and found 68% of participants to have subclinical evidence of translesional motor connections using surface electromyography.[148] Therefore, integration of injury severity with MRI would help establish the role of SCS in patients with a complete cut-off of the spinal cord.

Several studies did not distinctly report the device used or the stimulation details. This will help systematise research further. Different stages of research can be planned in such a way as to engage individuals with lived experiences of SCI to make sure that the results of SCS studies resonate with the critical concerns of the SCI community.[149] There is a requirement of comparative studies of two types of SCS. As per available literature there is limited evidence of multi-modal studies. Only two studies have assessed TSCS and ESCS together.[74,150] The results should report subject-reported outcomes as well.

Increasingly several studies suggest that persistent neuromodulation appears to persist following long-term ESCS use and TSCS interventions as short-term as two months, even after termination of active stimulation by ESCS or TSCS. In spite of several unanswered issues and a minimal understanding of the mechanisms of SCS, electrical neuromodulation has tremendous potential in the treatment of those living with SCI.

10. Study limitations

This review was limited to original clinical research available in the English language. To improve the data quality, we excluded conference proceedings, reviews, proposed research or protocol description, theses, abstracts, lectures, commentaries and editorials from this review. Due to the fragmentary nature of information, along with the variable use of terms, in particular, related to the devices used and stimulation characteristics, the data extracted are incomplete.

11. Conclusion

Significant advances in the investigation of the role of spinal cord electrical stimulation in the motor improvement of SCI patients have been achieved. However, high-quality studies have to be conducted to establish it as a standard of care. Further research has to be performed on the mechanism of SCS for other issues faced by SCI patients, such as pulmonary, genitourinary, and autonomic functions. Support of government agencies, funding agencies, and collaborative activities could go a long way in carrying out further

research on SCS, which has immense potential to drastically change the lives of individuals with SCI.

Ethical approval

No ethical approval was required for this study.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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