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Review Article

Epidural spinal cord stimulation for motor recovery in spinal cord injury: A systematic review

Conor McHugh[a,1], Clare Taylor[a,1], David Mockler[b,2] and Neil Fleming[a,2,*]

[a]*Human Performance Laboratory, Department of Anatomy, School of Medicine, Trinity College Dublin, Ireland*
[b]*John Stearne Medical Library, Trinity Centre for Health Sciences, School of Medicine, St. James's Hospital, Dublin, Ireland*

Abstract.
BACKGROUND: Epidural spinal cord stimulation (ESCS) emerged as a technology for eliciting motor function in the 1990's and was subsequently employed therapeutically in the population with spinal cord injury (SCI). Despite a considerable number of ESCS studies, a comprehensive systematic review of ESCS remains unpublished.
OBJECTIVE: The current review of the existing literature evaluated the efficacy of ESCS for improving motor function in individuals with SCI.
METHODS: A search for ESCS studies was performed using the following databases: Medline (Ovid), Web of Science and Embase. Furthermore, to maximize results, an inverse manual search of references cited by identified articles was also performed. Studies published between January 1995 and June 2020 were included. The search was constructed around the following key terms: Spinal cord stimulation, SCI and motor response generation.
RESULTS: A total of 3435 articles were initially screened, of which 18 met the inclusion criteria. The total sample comprised of 24 participants with SCI. All studies reported some measure of improvement in motor activity with ESCS, with 17 reporting altered EMG responses. Functional improvements were reported in stepping ($n = 11$) or muscle force ($n = 4$). Only 5 studies assessed ASIA scale pre- and post-intervention, documenting improved classification in 4 of 11 participants. Appraisal using the modified Downs and Black quality checklist determined that reviewed studies were of poor quality. Due to heterogeneity of outcome measures utilized in studies reviewed, a meta-analysis of data was not possible.
CONCLUSION: While the basic science is encouraging, the therapeutic efficacy of ESCS remains inconclusive.

Keywords: Spinal cord stimulation, spinal cord injury and motor response generation

1. Introduction

Across the globe, spinal cord injury (SCI) remains a thorn in the side of neurological medicine. With over 750,000 new cases each year, it is estimated that millions of people worldwide are grappling with the profound consequences of SCI (Kumar et al., 2018). Of those who survive the initial injury (4 to 15% mortality), only 36 to 42% of patients are ever discharged to their homes (Kumar et al., 2018; Smith et al., 2019). Despite the best efforts of the healthcare community to maximize rehabilitation and refine medical management, sufficient neuroplastic recovery remains elusive. For the most part, SCI patients will have an in-patient stay of up to three

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[1]Denotes graduate student author.

[2]Denotes professional author.

[*]Address for correspondence: Neil Fleming, E-mail: neil.fleming@tcd.ie.

months to optimize immediate post-injury neuroplasticity (Smith et al., 2018). Once rehabilitation has plateaued, these patients are then managed via adaptive devices and strategies to facilitate independent or assisted activities of daily living (Truchon et al., 2017).

Innovative technologies such as wearable robotics, brain-computer interfaces and stimulation devices are increasingly being examined as strategies for improving or assisting activities of daily living (ADLs) in neurological pathologies (Jackson & Zimmermann, 2012; Mekki, Delgado, Fry, Putrino, & Huang, 2018; van den Brand et al., 2015). Epidural Spinal Cord Stimulation (ESCS) is one such innovative strategy currently being explored. This technology first emerged as a method of relief for neurogenic back pain in the 1970's (Shealy, Mortimer, & Hagfors, 1970; Shealy, Mortimer, & Reswick, 1967). Following this, Cook and Weinstein (1973) made the chance discovery of motor activity during epidural stimulation for pain relief in patients with multiple sclerosis. Following these initial observations, ESCS was trialled in other motor conditions (Waltz, Reynolds, & Riklan, 1981).

The next major step explored the central pattern generator (CPG) in humans and possible applications of excitation in the SCI context (Bussel, Roby-Brami, Rémy Néris, & Yakovleff, 1996; Dimitrijevic, Gerasimenko, & Pinter, 1998). The CPG can be described as dedicated spinal circuitry producing rhythmic neural activation patterns that underlie locomotion in humans and other mammals (Minassian, Hofstoetter, Dzeladini, Guertin, & Ijspeert, 2017). The existence of the CPG in animals has been studied since it was initially identified in 1906 by Sir Charles S. Sherrington (Sherrington, 1906). In the last century, research has advanced from work on decerebated cats (Grillner & Rossignol, 1978; Grillner & Zangger, 1975) to animals with a more homonymous nervous system to our own, such as primates (Fedirchuk, Nielsen, Petersen, & Hultborn, 1998). Seminal works by Bussel et al. (1996) and Dimitrijevic et al. (1998) presented evidence for the first time of a CGP in humans. Dimitrijevic's study was the first to induce the CPG via ESCS in SCI patients. A number of additional studies emerged in the early 2000's investigating methods of stimulating the locomotor CPG via ESCS (Carhart, He, Herman, D'Luzansky, & Willis, 2004; Herman, He, D'Luzansky, Willis, & Dilli, 2002; Huang, He, Herman, & Carhart, 2006; Jilge et al., 2004; Minassian et al., 2013; Minassian et al., 2004). Of these, the first therapeutic study by

Herman et al. (2002) involved a single American Spinal Injury Association (ASIA) Impairment Scale C quadriplegic participant. Over a period of 4 months, ESCS combined with partial weight bearing therapy (PWBT) allowed the participant to graduate from predominantly wheelchair use and treadmill assisted walking, to overground walking (with a walker) independently. Furthermore, this case study reported that ESCS also enabled multiple ADLs at home and in the community.

Naturally, these encouraging results led to a growing number of published studies with similar outcomes (Carhart et al., 2004; Ganley, Willis, Carhart, & He, 2005). However, it was not until Harkema et al. (2011) combined ESCS with physical therapy to achieve independent standing in a single ASIA-A patient, that evidence was presented supporting efficacy in the motor complete SCI sub-group. This work indicated that, for the first time, spinal neuronal networks could be re-engaged by ESCS to produce meaningful motor output (Harkema et al., 2011). The sensory information provided by weight-bearing training was recognized by the spinal cord and utilized to generate measurable motor output; namely, EMG and ground reaction force, in the absence of supraspinal input. An investigation by Minassian et al. (2013) further supported this promising rehabilitation potential of ESCS when they described motor improvements following training seven motor complete SCI individuals with ESCS and assisted treadmill stepping (Minassian et al., 2013).

Advances in knowledge amongst the active research groups led to a greater level of refinement in the application of ESCS. The astute study design by Angeli et al. (2014) illustrated that SCI individuals could adapt their motor responses in accordance with the strength of auditory or visual cues. Their data provided evidence that some supraspinal control of motor responses was possible in the presence of ESCS. Furthermore, researchers have since realized the importance of participant-specific parameters for optimization of motor responses in a task dependent manner (Rejc, Angeli, & Harkema, 2015; Rejc, Angeli, Atkinson, & Harkema, 2017). Rejc et al. (2015) demonstrated that parameters optimized for one participant resulted in very different EMG patterns in others, insufficient to promote the same standing activity (Rejc et al., 2015). This individualized approach yielded impressive outcomes, most notably with one long-term participant who, over the course of 3.7 years of personalized ESCS training and rehabilitation, was able to stand independently

without ESCS (Rejc, Angeli, Atkinson, & Harkema, 2017).

As Harkema's and Rejc's studies were ongoing, parallel efforts by Grahn et al. (2017), Gill et al. (2018) and Calvert et al. (2019) were progressing at the Mayo Clinic. One of the many notable achievements of this group was the time course over which they produced clinical success. Grahn's patient was classified as T6 ASIA-A SCI, 3 years post-injury. Following 8 ESCS sessions over a two-week period, they accomplished voluntary control of task-specific muscle activity, independent standing and voluntary control of step-like activity while in a body weight supported position (Grahn et al., 2017). Gill et al. (2018) utilized a similar approach to Rejc et al. (2017). This 'multimodal rehab' with ESCS accomplished walking frame ambulation with minimal assistance in just 43 weeks.

Recent innovations in technology have provided researchers with greater control of ESCS delivery, allowing them to more effectively replicate the ebb and flow of an intact spinal network. Wagner et al. (2018) equipped their implanted pulse generator with real-time stimulation triggering capabilities, providing phase-dependent stimulation parameters. Up until this point in ESCS research, the method of delivery to the SCI population had been similar to the method used for management of chronic neuropathic pain. Stimulation waveforms usually comprised of continuous, non-patterned pulses as settings were derived from the intended goal of continually activating regions such as the dorsal columns to relieve the perception of pain (Wolter & Winkelmüller, 2012; Yampolsky, Hem, & Bendersky, 2012). Conversely, in the SCI population, continuous stimulation may inhibit and interfere with the rhythmic proprioceptive sensory signaling arriving at the spinal cord via weight bearing/stepping. Hence, the cultivation of temporal and spatially targeted spinal cord stimulation may temper proprioceptive interference while at the same time, selectively activate the sensorimotor networks needed for human locomotion (Formento et al., 2018). Indeed, this method delivered results far beyond what had been reported up to that point. Wagner's participants were capable of walking with gait aids and cycling independently in the community with their unique method of spatiotemporally modified ESCS (Wagner et al., 2018).

Overall, ESCS has emerged as a highly specialized and novel treatment that has the potential to evoke motor output, even in the most severe cases of SCI (Angeli et al., 2018). The number of studies has risen steadily over the course of the last decade (Angeli et al., 2014; Calvert et al., 2019; Gill et al., 2018; Wagner et al., 2018). However, to the best of our knowledge, the methodological approaches have not been summarized thus far, nor the outcomes evaluated formally. Therefore, the aim of the current review was to pool all of the currently available research regarding the efficacy of ESCS for regaining motor function in SCI, and systematically review existing methodologies and results.

2. Methods

2.1. Search strategy

The methodology described by the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (Moher et al., 2016) was adhered to for the current review. In consultation with a research librarian (DM), the most suitable electronic databases were chosen, and key search terms agreed upon. An exhaustive literature search was performed using four electronic databases (CINAHL, Embase, Medline, Web of Science). A search strategy and Medical Subject Headings (MeSH) was constructed around the following key terms: spinal cord stimulation, spinal cord injury and motor response generation. These search terms were expanded using a wide array of alternative terminologies, truncations and abbreviations. An inverse manual search of the bibliographies of all included full-text articles was also conducted. Filters were used to restrict the search to specific dates (January 1995 to June 2020), English language studies and human studies.

2.2. Study selection procedure

Eligibility criteria were formulated in accordance with the PICO model (Population, Intervention, Comparison, Outcome). In brief, the following inclusion criteria were established requiring: (1) Participants >18 years of age with a primary diagnosis of SCI and an Epidural Spinal Cord Stimulator surgically implanted, (2) Epidural stimulation aimed primarily at producing a motor response, (3) ESCS of a pulsed or continuous nature, (4) A clinical intervention design (Case study, Case series, Cohort study or Randomized controlled trial), (5) Studies including at least one reasonable measure of motor output (e.g. EMG, force), (6) Studies reporting data pertaining

to stimulation parameters, (7) Primary original data from an interventional study, and (8) Publication in English between January 1995 to June 2020. We excluded (1) Animal studies, (2) Participants <18 years of age, (3) Healthy participants, (4) Participants with other neurological disorders, (5) All other types of interventional electrical spinal cord stimulation, (6) Pain as the primary outcome, (7) Studies that failed to specify stimulation parameters, (8) Review articles, conference proceedings, expert opinions or any other secondary publications, (9) Full text or abstract unavailable and (10) Articles published before 1995. After retrieval of the initial search results, duplicates were removed by review-specific software (www.covidence.org). Following this, two independent reviewers (CM, CT) began pilot screening of 150 randomly selected articles to ensure clear interpretation of the exclusion criteria. This pilot screening process was repeated until a Cohen's Kappa >0.75 was achieved. Subsequently, the abstracts were screened by both reviewers using the criteria listed above and the reasons for exclusion were documented. Inter-operator agreement for abstract screening resulted in a Cohen's Kappa of 0.80. Following this, full texts were reviewed for inclusion and again, all reasons for exclusion recorded. The decisions of both reviewers were compared, and the inclusion or exclusion of disputed studies was discussed with a third reviewer (NF) until a clear consensus was reached. The literature search was last performed on the 30 June 2020.

2.3. Data extraction

Two independent reviewers completed a standardized spreadsheet designed in Excel in order to systematically extract the relevant data for review. Information was extracted regarding (1) Patient demographics, (2) Stimulation parameters, (3) Outcome measures related to motor output, (4) EMG methods and results, (5) Adverse events and (6) Repeat participants. Repeat participants were identified if the following three criteria were fulfilled: 1) The study referenced the participant in a previous study, 2) Age, ASIA classification and time since injury data matched the referenced participant in both studies and 3) majority of authors on the duplicate papers were consistent. Data extraction results were evaluated for accuracy and a third reviewer adjudicated to resolve any lack of consensus.

2.4. Methodological appraisal

The Modified Downs and Black Quality Checklist was used to assess the methodological quality of the included full texts (Downs & Black, 1998). Two independent reviewers conducted the quality appraisal. When disagreements occurred a third reviewer adjudicated until a consensus was reached. The Downs and Black Quality Checklist is a 27-item checklist that evaluates methodological strengths and weaknesses of articles based on the categories of (1) Reporting, (2) Internal validity (Bias), (3) Internal validity (Confounding), (4) External validity and (5) Power. The modified version differs from the original only regarding the final question of statistical power. Instead of rating according to a *post-hoc* calculation of study powers, a binary rating is used based on whether the study performed a power calculation or not. Downs and Black scores were subsequently awarded a quality rating based on previously published descriptors: excellent (26 to 28); good (20 to 25); fair (15 to 19); and poor ($\leq$14) (Hanada et al., 2020; Hooper, Jutai, Strong, & Russell-Minda, 2008; Munn, Sullivan, & Schneiders, 2010).

3. Results

3.1. Study selection

An initial screening yielded 3435 articles. A total of 1213 duplicate articles were subsequently removed. Following title and abstract screening, 40 articles were identified for full-text review. Of the 40 articles reviewed at full-text, 18 fulfilled all inclusion criteria. Of these 18 included studies, all were interventional case studies or case series. The selection of the studies followed the PRISMA guidelines (Moher et al., 2016). See Fig. 1 for the PRISMA diagram detailing the search process.

3.2. Participants

The total number of study participants evaluated in the current review was 40. However, 7 of these were identified as repeat participants in a minimum of two and a maximum of four studies, resulting in cumulative data presented on only 24 individuals. The majority were of a young age (34 ± 12 yr) and of male gender (73.7%). The mean ($\pm$ SD) time between SCI and study enrolment was 4.2 ($\pm$ 2.1) yr. In terms of injury severity, the most studied sub-group
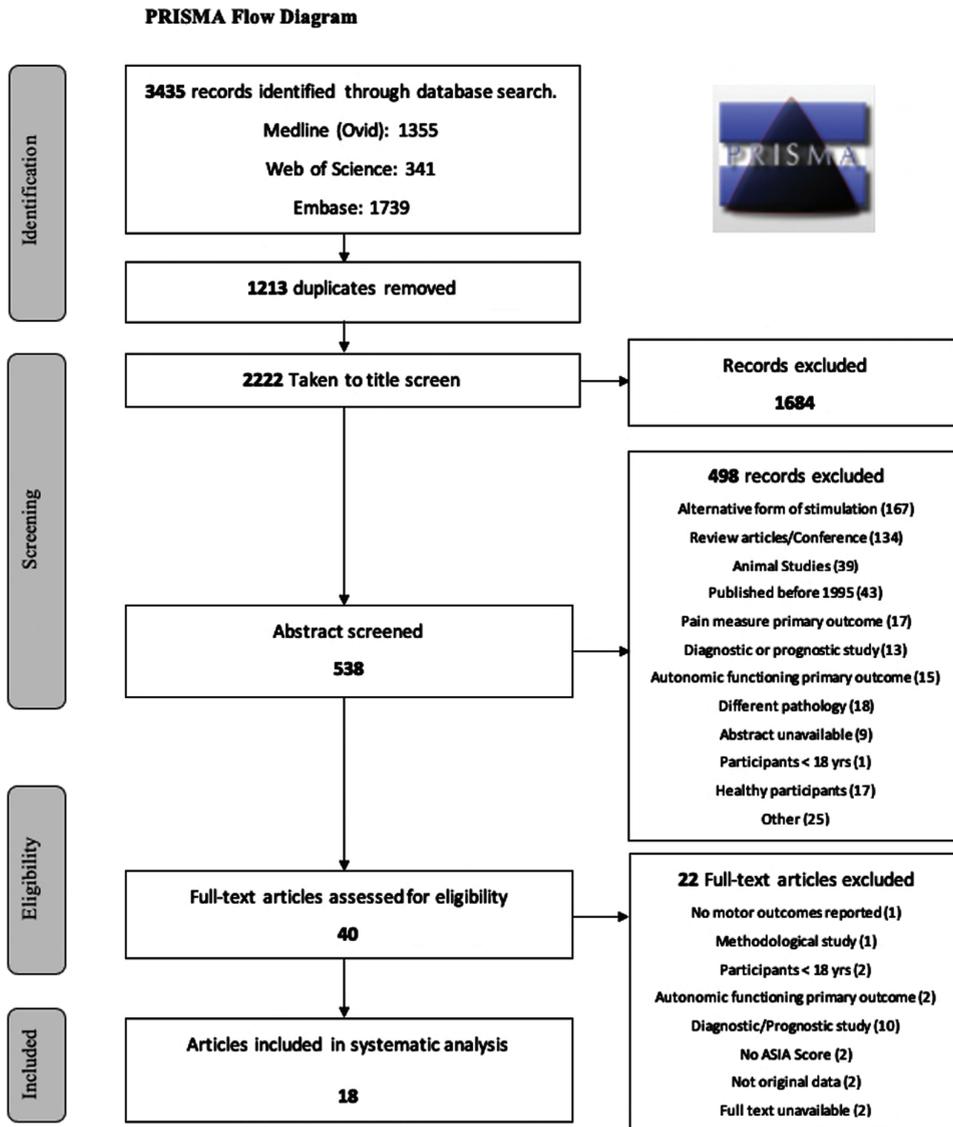
PRISMA Flow Diagram

Fig. 1. PRISMA Diagram (Moher et al., 2016).

were those with an initial classification of ASIA-A ($n = 11$), followed by ASIA-B ($n = 8$), ASIA-C ($n = 4$) and ASIA-D classifications ($n = 1$).

3.3. Methodological approach

All of the studies in this review were case studies or case series. Due to the heterogeneity of the outcome variables reported, a quantitative synthesis of methodological parameters was not possible. Therefore, a qualitative table was constructed outlining the intervention type, sample sizes, levels of injury, ASIA classifications, parameters selected and implant devices (Table 1). Training data were also

included in this table (frequency, intensity, time and type as available), as well as the last follow-up evaluation post-ESCS training, see Table 1. Described stimulation parameters (frequency, amplitude/ and mode of delivery) varied greatly. All but one of the included studies targeted the lower limbs via the CPG (T12-L2) to enable locomotor type activity. Lu et al. (2016) was the only study to use ESCS for the purposes of upper limb motor recovery.

3.4. Outcome measures

The motor outcome measures selected by the studies in this review varied greatly. EMG was employed

Table 1
Description of included studies

Study	Design	Interventions	Stimulator	Participant	Level	AIS	Parameters described	Implant site	Training details	Follow-up[†]
Angeli et al. (2018)	CS	Standard rehab, Locomotor Rehab, ESCS + Stand/Step training and BWST	Medtronic Specify: 16 electrode array. 5-6-5.	#1	T4	A	2–50 Hz, 450 μs, 2.5 – 5.7 V*	SS; L1-S1/S2	60 min, twice daily x 1week. Once daily x 49 weeks.	63 weeks (115 incl. medical hold)
				#2	T4	A	2–50 Hz, 450 μs, 1.8 – 4.0 V*		Twice daily x 13 weeks Once daily x 24 weeks.	41 weeks
				#3	C5	B	2–50 Hz, 450 μs, 1.7 – 2.5 V*		Twice daily for 17 weeks. Once daily x 23 weeks.	85 weeks
				#4	T1	B	2–50 Hz, 450 μs, 1.0 – 2.9 V*		Twice daily x 15 weeks. Once daily x 47 weeks. Once daily x 5 weeks. Twice daily x 19 weeks.	24 weeks
Angeli et al. (2014)	CS	Locomotor Rehab, ESCS + Step/stand training, ESCS + Home training	Medtronic Restore Advanced: 16 electrode array. 5-6-5.	B07	T2	B	30 Hz, 450 μs, 4.0 – 9.0 V*	SS; L1 – S1	80 stand sessions, 80 step sessions, daily home and stand sessions x 40 weeks	83 weeks
				A45	T4	A	25/40 Hz, 450/210 μs, 5.2 – 7.5 V*	VL; T11 – T12	80 stand sessions, 80 step sessions. Number of home sessions unclear	34 weeks
				B13	C7	B	30 Hz, 450 μs, 0.5 – 1.5 V*		80 stand sessions, 80 step sessions. Number of home sessions unclear	38 weeks
				A53	T5	A	30 Hz, 450 μs, 2.5 – 6.7 V*		80 stand sessions, 75 step sessions. Number of home sessions unclear	17 week
Calvert et al. (2019)	CS	Side lying stepping, motor tasks + ESCS.	Medtronic Specify: 16 electrode array. 5-6-5.	#1	T6	A	40 Hz, 210 μs, 3.5 – 10 V*, 6.4V referenced Stim for intentional control	VL; T11 – L1	–	3 weeks
				#2	T3	A	40 Hz, 210 μs, 2.5 10 V*, 7.3V referenced Stim for intentional control.		–	3 weeks
Carhart et al. (2004)	CR	Partial weight bearing treadmill training ± ESCS, overground walking ± ESCS	Pisces-Quad Plus: Quadripolar array X-trel 3470: implanted receiver	#1	C5-C6	–	Continuous monophasic pulse trains, 40–60 Hz, >500 μs, amplitude midpoint between sensory and motor threshold values*	SS; T8-L2 VL; T10-T12	150 sessions	–

CORRECTED PROOF

Table 1
(*Continued*)

Study	Design	Interventions	Stimulator	Participant	Level	AIS	Parameters described	Implant site	Training details	Follow-up[†]
Darrow et al. (2019)	CS	ESCS + Motor tasks	Tripole and Poclaim Elite, Abbott, Plano, TX – 16 contact paddle Electrode array	#1	T8	A	16 – 400 Hz, 200 – 500 μs, minimum 2 – 15 mA, position dependent*	SS: ~L2- S2	–	–
				#2	T4	A	16 – 400 Hz, 200 – 500 μs, minimum 2 – 15 mA, position dependent*	VL; T12 / SS: ~L2- S2	–	–
Ganley et al. (2005)	CS	PWBT + FES, ESCS + PWBT.	Referenced as per Carhart et al. (2004) and Herman et al. (2002)	#1	C5-6	C	20 – 60 μs, 800 μs, amplitudes between sensory and motor thresholds*	VL; T12 / SS: T10 – T12	–	–
				#2	T8	C	20 – 60 μs, 800 μs, amplitudes at motor threshold*	SS: T10 – T12	–	–
Gill et al. (2018)	CR	Locomotor rehab, ESCS + rehab incl. locomotor and PWBT, ESCS + home rehab	Specify 5-6-6, Medtronic, 16 – contact electrode array	#1	T6	A	15 – 40 Hz range (20 – 25 Hz reported in figures), 210 μs, 2.5 – 6 V*.	SS: L2 – S1 / VL: T11 – L1	113 multimodal sessions and 43 home-based sessions over 43 weeks	43 weeks
Gorgey et al. (2020)	CR	ESCS + Exoskeleton rehab	Restore ADVANCED Medtronic, 16 – electrode array.	#1	C7	A	40 Hz, 420 μs, 4.4 – 8 V*	SS: T12 – S2 / VL: L1 – L2	24 sessions over 12 weeks (up to 75 mins per session).	13 weeks
Grahn et al. (2017)	CR	Motor training (incl. BWST), ESCS + Motor training (incl. BWST).	Medtronic RestoreSensor – Surescan 16 electrode array (specify 5-6-5)	#1	T6	A	24 – 40 Hz, 210 μs, 0 – 6 V (for volitional control and stepping). 15 Hz, 210 μs, 0 – 6 V (for standing).	Lumbar enlargement	8 sessions (5 – 7 hours) over 2 weeks	5 weeks after surgical implant
Harkema et al. (2011)	CR	Locomotor rehab + BWST, ESCS + motor rehab.	RestoreADVANCED, Medtronic: 16 electrode array (Specify 5-6-5).	#1	C7	B	5 – 40 Hz, 210 or 450 μs, 0.5 to 10 V* (15 Hz; standing, 30–40 Hz; stepping)	SS: L1 – S1 / VL: T11-L1	80 sessions, 60 – 250 min in duration (Mean ± SD; 54 ± 13),	7 months

(*Continued*)

Table 1
(*Continued*)

Study	Design	Interventions	Stimulator	Participant	Level	AIS	Parameters described	Implant site	Training details	Follow-up[†]
Herman et al. (2002)	CR	PWBT, ESCS + PWBT rehab.	Pisces – Quadplus Medtronic, X-TREL stimulation system.	#1	C5 – C6	C	20 – 60 Hz, 800 µs, amplitude above sensory threshold but below motor threshoold*.	Upper lumbar enlargement	12 weeks	12 weeks
Huang et al. (2006)	CS	ESCS + PWBT	PISCES – Quad Plus electrode, X-TREL stimulation system	#1	C5-6	C	20 and/or 40 Hz, 800 µs, 5.0 –8.5 V (between motor and sensory threshold)	SS: T10 – L2	–	–
				#2	T8	C	20 and/or 40 Hz, 800 µs, 3.0 – 3.5 V (between motor threshold and sensory threshold)	SS: T10 – L2	–	–
Lu et al. (2016)	CS	ESCS + task specific motor rehab	Boston Scientific Precision Plus/ Artisan spinal cord stimulator – 16 electrode array.	A1	C5	B	2 – 40Hz, 210 µs, 0.1 – 10mA*	C5-T1	20 sessions over 8 weeks ESCS for 60 mins in 180 min session	8 weeks
				A2	C6	B	2 – 40Hz, 210 µs, 0.1 – 10mA*	C5-T1	22 sessions in 7 days ESCS for 60 mins in 180 min session	7th day
Moshonkina et al. (2012)	CS	Locomotor rehab, ESCS + rehab/ locomotor rehab.	Cooner Wire Co. w363A Stimulator	K.S.	T7	A-B	1–12 Hz	SS: L2-L4, S2	–	4 weeks
				S.A.	C5-7	A-B			–	2 weeks
				T.P.	T8-L1	B			–	Post-surgery only
				T.A.	L1	B-C			–	4 weeks
Rejc et al. (2015)	CS	Locomotor rehab, ESCS + Stand training with custom frame	Medtronic Restore Advance: 16 electrode array (5-6-5 Specify)	B07	T2	B	2–60Hz, 1.0 – 10.0 V (or near motor threshold)*	SS: L1-S1 VL: T11 – L1	80 sessions (60 min, 5 per week)	–
				A45	T4	A			80 sessions (60 min, 5 per week)	–
				B13	C7	B			80 sessions (60 min, 5 per week)	–
				A53	T4	A			80 sessions (60 min 5 per week)	–

Table 1
(Continued)

Study	Design	Interventions	Stimulator	Participant	Level	AIS	Parameters described	Implant site	Training details	Follow-up[†]
Rejc et al. (2017a)	CR	Locomotor rehab, ESCS + standing/step training + BWST.	Medtronic Restore Advanced: 16 electrode array (5-6-5 specify)	B13	C7	B	Standing; 40 – 60 Hz, 0.6 – 1.0 V*. Stepping; 30 – 55 Hz, 0.7 – 3.5 V*. Voluntary activity: 30 – 65 Hz, 0.4 – 2.2 V*	SS: L1-S1 VL: T11 – L1	160 sessions over 9.5 months (60 min per day). 60 min per day for 12 months at home. 60 sessions over 3 months (120 min per day). 60 min per day at home for 14 months. 100 sessions over 5.5 months (60 min per day).	44 months
Rejc et al. (2017b)	CS	Locomotor rehab, ESCS + standing/step training + BWST.	Medtronic Restore Advanced: 16 electrode array. 5-6-5.	B07	T2	B	2 – 60 Hz, 0.1 – 10.0 V*	SS: L1-S1 VL: T11 – L1	166 sessions (60 min, 5 per week)	Approx. 45 – 50 weeks
				A45	T4	A	Near motor threshold		160 sessions (1 hr, 5 per week)	Approx. 45 – 55 weeks
				B13	C7	B			161 sessions (1 hr, 5 per week)	Approx. 45 weeks
				A53	T4	A			161 sessions (1 hr, 5 per week)	Approx. 50 weeks
Wagner et al. (2018)	CR	ESCS + Rehab including BWST, overground locomotion and biking (aided by time adapted algorithms for delivery of ESCS).	Specify™ 5-6-5 surgical lead and implantable pulse generator, Medtronic	#1	C7	C	pulsed, 300μs, 20 – 120Hz, 0 – 16mA	SS: L1 – S2	5 months of training. Unclear frequency and duration.	5 months
			Specify™ 5-6-5 surgical lead and implantable pulse generator, Medtronic	#2	C4	D	Highly varied spatiotemporal parameters	SS: L1 – S2	5 months of training.	5 months
			Specify® SureScan® MRI 5-6-5 and implantable pulse generator, Medtronic.	#3	C7	C	Increasing frequency enhanced flexion	SS: L1 – S2	5 months of training.	5 months

Methodological appraisal of each study by Intervention type, Participant, Level of injury, ASIA classification, Stimulation parameters, Implant device, training details and follow-up. *Examples/ ranges of stimulation parameters were provided and spatiotemporal mapping was used to determine person and task specific configuration of parameters after initial assessments. †Follow-up time point: Defined as the last evaluation post-ESCS training. Abbreviations: AIS; ASIA Impairment Scale Score, BWST: body weight supported training, CR; case report, CS; case series, ESCS; epidural spinal cord stimulation, PWBT; partial weight bearing therapy, SCI; Spinal cord injury, SS; spinal segment, VL; vertebral level.

by seventeen of the eighteen studies. Gait-related measures; namely, velocity and/or distance were collected by eight studies (Angeli et al., 2018; Carhart et al., 2004; Ganley et al., 2005; Gill et al., 2018; Herman et al., 2002; Huang et al., 2006; Moshonkina et al., 2012; Wagner et al., 2018). However, only two studies utilized clinically validated walking tests; namely the 6-minute walk test or 10 metre walk test (Herman et al., 2002; Wagner et al., 2018). Formalised muscle force evaluations were reported in four studies (Angeli et al., 2018; Angeli et al., 2014; Lu et al., 2016; Wagner et al., 2018). A full list of outcome measures is documented in Table 2.

3.5. Evidence of motor recovery

ASIA classification both pre- and post-intervention was reported by five studies (Angeli et al., 2018; Gill et al., 2018; Grahn et al., 2017; Lu et al., 2016; Wagner et al., 2018). Examining these five studies, three outlined the motor and sensory scores in detail (Table 3). Re-categorisation of ASIA score post-ESCS was achieved by four participants. It should be noted however, that both participants in the study reported by Lu et al. (2016) were re-categorised via an assessment with ESCS applied, an approach which was not reported at baseline assessment.

Table 4 outlines the level of functional motor recovery achieved by each study. The categories reflect the common goal in the majority of the reviewed studies, that is, to achieve ambulation. The most basic category is volitional motor activity (VMVT) such as voluntary isometric force or joint movement, followed by assisted function (ambulation and standing) and finally independent function (ambulation and standing). The number of participants and their ASIA classifications are also provided to give context to the reader. Independent ambulation with a gait aid (crutches/walker) was reported by four of the 18 studies (Carhart et al., 2004; Ganley et al., 2005; Herman et al., 2002; Wagner et al., 2018).

3.6. Electromyography

With the exception of Herman et al. (2002), all other studies ($n = 17$) presented some form of EMG data as an indirect estimate of ESCS's impact on motor function. Table 5 provides a description of the EMG recording and signal processing methods employed, along with a synopsis of the corresponding output presented by each study. Overall, the high degree of variability in recording and signal processing

techniques was notable. Despite a large number of studies reporting some form of signal rectification and averaging ($n = 12$), an equal number ($n = 12$) presented exemplary raw EMG traces performed during VMVT (Angeli et al., 2014; Calvert et al., 2019; Lu et al, 2006; Moshinka et al., 2012; Rejc et al., 2015; Rejc et al., 2017a), assisted gait and/or standing (Gill et al., 2018; Rejc et al., 2017b, Wagner et al., 2018), or a combination of VMVT and gait/standing (Angeli et al., 2018; Grahn et al., 2017; Harkema et al. 2011). This output provides a useful, if somewhat limited, qualitative comparison of ESCS on and off ($n = 8$), level of muscle contraction ($n = 2$) or baseline compared to follow-up visits ($n = 3$). A total of four studies presented muscle activity during gait movements, using the more widely accepted format of EMG linear envelopes which have been amplitude normalised and averaged over a number of gait cycles (Carhart et al., 2004; Ganley et al., 2005; Gorgey et al., 2020; Huang et al., 2006). The resultant traces offer a clearer qualitative description of muscle activity during stepping movements with and without ESCS. Five studies did attempt some form of quantitative comparison in EMG response (Gill et al., 2018; Calvet et al., 2019; Rejc et al., 2015; Rejc, Angeli, Bryant, & Harkema, 2017; Wagner et al., 2018). However, given the very small sample size ($n = 1$ to 4) and in some cases the quantitative methods used, caution should be aired when interpreting these results.

3.7. Methodological quality

Results from the modified Downs and Black Quality Checklist are presented in Table 6. While all 18 of the studies reviewed were categorised into the poor range (<14) (Hanada et al., 2020; Hooper et al., 2008; Munn et al., 2010), a chronological trend towards improving quality was observed. Lu et al. (2016) achieved the highest score and represented the only upper limb study (13/28). The highest score achieved by lower limb studies (10/28) was shared between four studies (Darrow et al., 2019; Rejc et al., 2017a; E. Rejc et al., 2017b; Wagner et al., 2018).

3.8. Adverse events

Reported adverse events in this review were very rare, with just one study reporting a hip fracture (Angeli et al., 2018). However, it should be noted that fourteen of the included studies failed to report any information regarding adverse events or lack thereof.

Table 2
Outcome measures

Study	ASIA	Gait distance	Gait speed	PLOA gait	PLOA standing	% Body weight during gait	% Body weight during standing	GRF	Joint/ Muscle force	Joint kinematics (ROM)	No. of unassisted/ assisted steps	OG walking unassisted/ assisted	Treadmill walking unassisted/ assisted	Unassisted/ assisted standing (±time)	EMG	Intentional control of motor activity	Muscle mass	ARAT
Angeli et al. (2018)	X	X	X						X			X			X			
Angeli et al. (2014)									X						X	X		
Calvert et al. (2019)										X					X	X		
Carhart et al. (2004)	X	X	X			X				X					X			
Darrow et al. (2019)															X	X		
Ganley et al. (2005)		X	X			X				X		X			X			
Gill et al. (2018)	X	X	X	X	X	X		X			X	X	X	X	X			
Gorgey et al. (2020)				X							X	X		X	X			
Grahn et al. (2017)	X			X										X	X	X		
Harkema et al. (2011)					X	X	X	X		X					X	X		
Herman et al. (2002)		X	X									X						
Huang et al. (2006)		X	X			X				X		X			X			
Lu et al. (2016)	X								X						X			X
Moshonkina et al. (2012)			X												X			
Rejc et al. (2015)					X			X						X	X			
Rejc et al. (2017a)								X		X				X	X	X		
Rejc et al. (2017b)					X			X						X	X			
Wagner et al. (2018)	X	X	X	X		X		X	X	X	X	X	X		X	X	X	

Overview of outcome measures related to motor recovery. ARAT; Action research arm test, EMG; Electromyography, GRF; Ground reaction force, OG; Over ground, PLOA; Physical level of assistance.

Table 3
ASIA score at baseline and post-ESCS interventions

Study	Participant	Pre-ESCS			Post-ESCS		
		ASIA	Total Motor Score	Total Sensory Score	ASIA	Total Motor Score	Total Sensory Score
Angeli et al. (2018)	# 1	A	50	–	A	50	88
	# 2	A	50	–	A	50	90
	# 3	B	23	83	C*	24/25[†]	86
	# 4	B	50	–	B	50	134
Gill et al. (2018)	# 1	A	–	–	A	–	–
Grahn et al. (2017)	# 1	A	–	–	A	–	–
Lu et al. (2016)	# 1	B	9	37	[C*]	39	153
	# 2	B	17	46	[C*]	37	141
Wagner et al. (2018)	# 1	C	60	108	D*	77	106
	# 2	D	56	130	D	69	157
	# 3	C	45	83	C	51	85

Individual ASIA scores pre- and post-intervention. Total motor score out of 100 (R + L). Total sensory score out of 224 (R + L). *Indicates change of classification from baseline. [†] Conflicting score in paper (24) versus supplementary material (25). Square parentheses indicate ASIA evaluation performed with ESCS stimulation on (Lu et al., 2016).

Table 4
Motor recovery by highest level of function achieved

	ASIA	Volitional Activity	Assisted Function		Independent Function	
			Standing	Stepping	Standing	Stepping
Angeli et al. (2018)[†]	2B	X		X	X	
	2A	X	X	X		
Angeli et al. (2014)	2A, 2B	X				
Calvert et al. (2019)	2A	X				
Carhart et al. (2004)	1C	X				X
Darrow et al. (2019)	2A	X				
Ganley et al. (2005)	2C	X				X
Gill et al. (2018)	1A	X		X	X	
Gorgey et al. (2020)[‡]	1A	X		X		
Grahn et al. (2017)	1A	X		X	X	
Harkema et al. (2011)	1B	X	X	X		
Herman et al. (2002)	1C	X				X
Huang et al. (2006)	2C	X		X		
Lu et al. (2016)*[†]	2B	X				
Moshonkina et al. (2012)	2A, 2B	X		X		
Rejc et al. (2015)	2A	X			X	
	2B	X	X			
Rejc et al. (2017a)	1A	X			X	
Rejc et al. (2017b)	2A, 2B	X			X	
Wagner et al. (2018) [†]	2C 1D	X			X	X

Motor recovery by highest level of function achieved within each study is presented (note not all participants achieved this maximum level). Volitional motor activity – Classified as limb movement or visible motor contractions. Assisted function – Classified as ambulation/standing with an assistive device (E.g. walking frame, harness etc) and/or physical assistance by therapist/trainer in a laboratory setting. Independent function – Ambulation Classification: Ambulation with an assistive device but without physical assistance from a therapist or trainer in a community and/or home setting. Standing classification: Standing without physical assistance from a therapist or trainer/body weight support+/– own support using an assistive device in a laboratory setting. * Lu et al., (2016) was an upper limb study. Functional improvements in UL were reported. [†]Denotes a study where an ASIA classification upgrade was achieved. [‡] Denotes exoskeleton utilization in combination with ESCS

4. Discussion

4.1. Summary of findings

This review identified a total of 18 studies that evaluated ESCS for improvement in motor function in 24 separate individuals with SCI. Thirteen of these studies included motor-complete SCI patients, with the remaining five reporting on motor incomplete patients. All studies reported some level of functional improvement, with eleven studies describing improved locomotor function, eight studies reporting

Table 5
EMG recordings

Study	PREPARATION/RECORDING				SIGNAL PROCESSING			RESULTS
	Muscles [Preparation described*]	Response type [Action]	Recording device [Frequency]	Filter Hi/Lo [Stim artefact filtration]	Rectification	Cycle averaging	Amplitude normalization	Output presented
Angeli et al. (2018)	**Surface:** S, MG, TA, MH, RF, VL, GM, EXOB, ES, RA. **Fine wire:** IL. [**X**]	Dynamic [Gait + VMVT]	Motion Lab Systems (HW) [2 kHz]	High pass Butterworth (2 Hz) / Lo pass (NS) [✓ paraspinal]	FWR	Cycles not specified. Foot switches used for gait (normalized to step cycle).	–	Exemplary raw EMG traces for gait, standing and VMVT. Rectified EMG trace time normalized to gait for one participant. Qualitative comparison of stim on/off.
Angeli et al. (2014)	**Surface:** S, TA, MH, VL, AM, GM, 6th IC. **Fine wire:** IL, EHL, EDL. [**X**]	Dynamic [Gait + VMVT. Isometrics]	Motion Lab Systems (HW) [2 kHz]	High pass (32 Hz) / Lo pass (NS) [✓ paraspinal]	–	–	–	Exemplary raw EMG traces for VMVT. Exemplary iEMG data for IL, AD, IC, AM muscles. Qualitative comparison of varying force contractions.
Calvert et al. (2019)	RF, VL, MH, TA, MG, S. [**X**]	1. Evoked 2. Dynamic [VMVT]	ADInstruments PowerLab [4 kHz]	Notch (60 Hz) and bandpass filters (20 – 1000 Hz). [✓ paraspinal]	RMS (Window: 200 samples, Overlap: 50 samples)	Mean/SD data calculated from 5 consecutive stimuli.	–	Quantitative comparison of stim configuration and intensity for evoked responses. Exemplary raw EMG trace for gravity neutral stepping.
Carhart et al. (2004)	VM, RF, BFLH + SH. No ankle due to AFO. [✓]	Dynamic [Gait + VMVT]	Noraxon MyoSystem 2000 [1 kHz]	High (10 and 15 Hz)/low pass (500) (BW 2nd order, – 3 dB). [✓ Proximal electrode]	FWR	Mean of 200 samples represented in Fig 4. Mean of 32 –54 gait cycles represented in Fig 5.	Peak dynamic method	Average rectified EMG traces amplitude normalized to peak data and time normalized to gait cycle. Qualitative comparison with ESCS on/off.
Darrow et al. (2019)	RA, T10 IC, T12 PS, IL, RF, TA, EHL, G. [**X**]	Dynamic [VMVT]	Natus Nicolet Electrodiagnostic System [NS]	Butterworth (4th order). [–]	RMS but unclear method to generate "response magnitude component"	Averaged over 3 attempts of each BMCA manoeuvre.	–	Quantitative comparison of "Response magnitude component" of Net EMG Power with ESCS on/off. Raw EMG traces during VMVT.

(Continued)

Table 5
(*Continued*)

Study	PREPARATION/RECORDING					SIGNAL PROCESSING		RESULTS
	Muscles [Preparation described*]	Response type [Action]	Recording device [Frequency]	Filter Hi/Lo [Stim artefact filtration]	Rectification	Cycle averaging	Amplitude normalization	Output presented
Ganley et al. (2005)[†]	VM, RF, BFLH, SH. No ankle due to AFO. [✓]	Dynamic [Gait]	Noraxon MyoSystem 2000 [1 kHz]	High/low pass (10 and 15 Hz) (BW 2nd order, −3 dB). [✓ Proximal electrode pair.]	FWR	Time normalized using ipsilateral foot-foot contact interval. Number of cycles not specified.	Peak dynamic method	Average rectified EMG traces amplitude normalized to peak data and time normalized to gait cycle. Qualitative comparison of ESCS on/off.
Gill et al. (2018)	RF, VL, MH, TA, MG, S. [✗]	Dynamic [Gait, Standing, VMVT]	PowerLab AD instruments [4 kHz]	Notch filter (60 Hz) and bandpass (BW 20–1,000 Hz) [–]	RMS (Window: 600 samples, Overlap: 200 samples).	EMG RMS values from 10 cycles per leg were averaged for each muscle.	Mean dynamic method	Exemplary raw and rectified EMG traces during gait. Normalized EMG quantitatively compared within phases of the gait cycle. CV qualitatively compared for standing and VMVT.
Gorgey et al. (2020)	QU, Hams, S, GM, GL. [✗]	Dynamic [Gait]	Delsys Trigno [2 kHz]	Bandpass (BW 4th order, 20–450 Hz. [–]	RMS (Window: 150 samples for 10 strides)	Averaged RMS envelopes over 10 strides. Time normalized via IMU data from MG sensor.	Mean dynamic method	Average rectified EMG traces amplitude normalized to mean data and time normalized to 10 gait cycles. Qualitative comparison of baseline and post-intervention with ESCS on/off with cross-correlation.
Grahn et al. (2017)[‡]	RF, VL, MH, TA, MG, S. [✗]	Dynamic [Gait, Standing, VMVT]	PowerLab AD instruments [4 kHz]	Notch filter (60 Hz) and bandpass (BW 20–1,000 Hz) [–]	RMS (window: 4000 samples, overlap: 3000).	Average of 3–5 trials of the selected task. Time normalization unspecified.	Peak dynamic method	Exemplary raw and rectified EMG traces during VMVT and standing. Qualitative comparison of stim on/off and voluntary EMG over time.
Harkema et al. (2011)	**Surface**: S, MG, TA, MH, QU, GM **Fine wire**: IL [✗]	Dynamic [Gait, Standing, VM]	Motion Lab Systems [2 kHz]	Not specified [✓ Paraspinals]	–	Not specified	–	Exemplary raw EMG traces during gait, standing and VMVT. Qualitative comparison of mean EMG stim on/off during sitting and standing.

CORRECTED PROOF

Study	Muscles	Task	EMG System	High/Low pass filter	FWR	Averaging method	Analysis
Huang et al. (2006)	VM, RF, BFLH, SH. No ankle due to AFO [✓]	1. Evoked 2. Dynamic [Gait]	Noraxon MyoSystem 2000 [1 kHz]	High/Low pass filtered at 10/500 Hz. [–]	FWR	Averaged EMG amplitudes for 10 stride cycles. Time normalization to gait (via motion capture and plantar foot pressure). Peak dynamic method.	Average rectified EMG traces amplitude normalized to peak data and time normalized to gait cycle with ESCS on/off. Time frequency analysis of EMG in relation to ESCS stimulation.
Lu et al. (2016)	PS, D, BB, TRB, BR, ED, FD, TE, THE. [✓]	1. Evoked 2. Dynamic [VMVT]	T50 Myopac Wireless System, Konigsberg Instruments [10 kHz]	10 Hz to 5 kHz [–].	–	For evoked, 20 potentials averaged.	Exemplary raw EMG traces during hand-grip task. iEMG trace included for FD muscle evoked response. Qualitative comparison of stim on/off during hand-gripping.
Moshonkina et al. (2012)	BF, QU, G, TA. [✗]	Dynamic [VMVT]	EMGST-1 [NS]	Not specified [–]	–	Average of 25 cycles for amplitude average but no clear presentation of that data.	Exemplary raw EMG traces during VMVT. Qualitative comparison of stimulation frequency and time since implantation.
Rejc et al. (2015)	**Surface:** GM, MH, RF, VL, TA, MG, S. **Fine Wire:** IL [✗]	1. Evoked 2. Dynamic [Stand, Sit-to-Stand]	Not specified [2 kHz]	Not specified [✓ Paraspinals]	–	Not specified for STS or standing. Average of 15 or 100 potentials for evoked responses	Exemplary raw EMG traces during VMVT with. Qualitative comparison of stim on/off. Amplitude of evoked response. Quantitative comparison of stim configuration.

(Continued)

Table 5
(*Continued*)

Study	PREPARATION/RECORDING					SIGNAL PROCESSING		RESULTS
	Muscles [Preparation described*]	Response type [Action]	Recording device [Frequency]	Filter Hi/Lo [Stim artefact filtration]	Rectification	Cycle averaging	Amplitude normalization	Output presented
Rejc et al. (2017a)	**Surface** - GM, MH, RF, VL, TA, MG, S, SCM, 6th IC. **Fine Wire** – IL [X]	Dynamic [Stand, Sit-to-stand, VMVT]	Not specified [2 kHz]	Not specified [–]	RMS	Not specified	RMS EMG activity during task divided by background RMS amplitude.	Exemplary raw EMG traces during VMVT. Normalized EMG qualitatively compared over 8 session time-points. Probability density distribution of MH and VL muscles to qualitatively evaluate co-contraction.
Rejc et al. (2017b)	**Surface** - GM, MH, RF, VL, TA, MG, S. **Fine Wire** – IL [X]	Stand, Sit-to-stand. Evoked	Not specified [2 kHz]	Low pass filter (4 Hz) [✓ Paraspinals]	RMS	5–20 stimuli average for evoked responses	–	Exemplary raw EMG traces during standing and stepping. CV for data to examine variability in muscle activity. Amplitude of evoked response with quantitative comparison of pre-, post-stand and post-step training.
Wagner et al. (2018)	IL, RF, VL, ST, BF TA, MG, S. [X]	Gait, Isometric, VMVT, evoked.	Myon 320 System [1 – 5 kHz]	Band-pass 10 and 450 Hz (BW 4th order filter). [✓ Paraspinals]	RMS: 500 ms window (VMVT). RMS 250 ms window (Gait)	Averaged over a variable number of steps. Synchronized to gait platform.	RMS EMG normalised to 250 ms moving average window.	Exemplary raw EMG traces during VMVT, standing and stepping. Amplitude of evoked response compared to stimulation intensity. Normalized EMG compared to stim amplitude and frequency.

EMG recording and signal processing table. *Preparation - In order receive a yes (✓) for this criterion the paper needed to describe: Skin preparation, orientation and location of electrodes, electrode shape/composition and inter-electrode distance. An omission of any of these details resulted in a no (X) being awarded. †Ganley et al., 2005 referenced Carhart et al., 2004 for all EMG data. ‡Grahn et al., 2017: supplementary data was unavailable. BB: Bicep Brachii; BFSH/BFLH: Biceps Femoris Long Head/Short Head, BR; Brachioradialis, BW; Butterworth, CV; Coefficient of variation, D; Deltoid, ED; Extensor digitorum, EXOB; External Oblique, FD; Flexor digitorum, FWR; full wave rectification, G; Gastrocnemius, GM; Gluteus Maximus, HAMS; Hamstrings, HW; Hard wired, IC; Intercostal muscles, iEMG; integrated electromyography, IL; Iliopsoas, IMU; inertial measurement unit, GL; Lateral Gastrocnemius, MG; Medial Gastrocnemius, PS; Paraspinals, QU; Quadriceps, RA; Rectus Abdominus, RF; Rectus Femoris, RMS; Root mean squared, S; Soleus, SCM; Sternocleidomastoid, SM; Semimembranosus, ST; Semitendinosus, TA; Tibialis Anterior, TE; Thenar Eminence, THE; Hypothenar Eminence, TRB; Triceps Brachaii, VL; Vastus Lateralis, VM; Vastus Medialis, VMVT; Voluntary movement, W; Wireless.

improved standing ability and one study (Lu et al. 2016) describing improved upper limb function (Table 4). The ASIA impairment scale is currently the most widely accepted clinical classification system for SCI and forms the standard basis for measuring neurological outcomes (Alizadeh, Dyck, & Karimi-Abdolrezaee, 2019; Steeves et al., 2007). Clinical evaluations of sensorimotor functioning using this scale were reported post-intervention in five studies. A total of four participants ($n = 4$), in three of these reviewed studies, improved their overall classification (Table 3). One participant from Angeli et al. (2018) and two participants from Lu et al. (2016) were reclassified from ASIA-B to ASIA-C, while one participant from Wagner et al. (2018) was reclassified from ASIA-C to ASIA-D. Changes in EMG motor response were reported by all studies, with the exception of Herman et al. (2002). However, inconsistencies in the reported methods and presentation of EMG data limit any meaningful interpretation. The overall quality of the literature was poor (Downs & Black scores ranging from 4/28 to 13/28), with all papers being either case studies or case series. Considering the technological and logistical feasibility of research of this type, the reported lack of quality is unsurprising. However, chronological analysis is encouraging (Table 6) and suggests a trend towards improving quality, as study designs become more refined and robust.

4.2. Evidence of efficacy

The variability in outcome measurement and the limited sample size preclude a categorical declaration of efficacy at this point. Despite this, there are promising elements found by this review that warrant further attention. Namely, improvements in ASIA scoring reported in three studies (Angeli et al., 2018; Lu et al., 2016; Wagner et al., 2018). The total motor scores of Wagner's three participants rose by 17, 13 and 6 points (Wagner et al., 2018). In Angeli et al. (2018) one participant out of three reported on, bettered their baseline motor score from 23 to 24/25 (Table 3). In contrast, Lu et al. (2016) chose to reassess their participants with ESCS switched on. Both participants enhanced their total motor scores from 9 to 39 and 17 to 37, respectively. Of these three studies (Angeli et al., 2018; Lu et al., 2016; Wagner et al., 2018), the improvements in motor scores were sufficient for the ASIA classification to be changed for four participants.

While clinical evaluations are useful for researchers and clinicians, functional abilities for daily activities have been noted as the most meaningful and valued outcomes for individuals living with SCI (Steeves et al., 2007). Improvement in EMG output without translation into function for example, offers little to improve the life of an individual with SCI. In this respect, ESCS has displayed some positive results. Four studies achieved independent ambula-

Table 6
Modified Downs and Black quality appraisal

Study	Reporting (0/12)	External validity (0/3)	Internal validity (0/6)	Selection bias (0/6)	Power (0/1)	Total (0/28)
Herman et al. (2002)	3	0	2	0	0	**5**
Carhart et al. (2004)	6	0	2	0	0	**8**
Ganley et al. (2005)	3	0	1	0	0	**4**
Huang et al. (2006)	5	0	2	0	0	**7**
Harkema et al. (2011)	3	0	1	0	0	**4**
Moshonkina et al. (2012)	4	0	1	0	0	**5**
Angeli et al. (2014)	5	0	1	0	0	**6**
Rejc et al. (2015)	4	0	1	0	0	**5**
Lu et al. (2016)	8	0	5	0	0	**13**
Grahn et al. (2017)	4	0	1	0	0	**5**
Rejc et al. (2017a)	8	0	2	0	0	**10**
Rejc et al. (2017b)	8	0	2	0	0	**10**
Angeli et al. (2018)	4	0	3	0	0	**7**
Gill et al. (2018)	5	0	2	0	0	**7**
Wagner et al. (2018)	7	0	3	0	0	**10**
Calvert et al. (2019)	6	0	3	0	0	**9**
Darrow et al. (2019)	7	0	3	0	0	**10**
Gorgey et al. (2020)	2	0	3	0	0	**5**

Results from the Modified Downs and Black quality appraisal presented in chronological order.

tion with gait aids in the community and/or home setting (Carhart et al., 2004; Ganley et al., 2005; Herman et al., 2002; Wagner et al., 2018). While these impressive results were achieved in motor incomplete individuals, it still represents a significant easing of ADL difficulty for each participant. This is perhaps the strongest evidence to support efficacy of ESCS currently.

4.3. Study participants

The majority of participants were male ($n = 14$), in keeping with the higher incidences of SCI in the men (Smith et al., 2019; Smith et al., 2018). Study participants varied most notably in terms of ASIA classification and time since injury. Despite early and impressive results reported in motor incomplete SCI participants (Carhart et al., 2004; Ganley et al., 2005; Herman et al., 2002), most participants in the current review were motor complete (ASIA-A and B, $n = 19$), while only five participants with residual motor abilities were studied (ASIA-C and D, $n = 5$). Despite the imbalanced number of studies which have thus far evaluated ESCS in motor-complete patients (Table 3 and 4), the results from the current review would generally point towards greater efficacy in individuals with some residual motor function.

Time since injury (4.2 ± 2.1 yr) was highly variable between studies; however, all participants at the time of recruitment were in the chronic stage of SCI, where substantial muscle atrophy has already occurred (Gorgey & Dudley, 2007; Kern et al., 2008). As of yet, no study has examined the use of ESCS in the acute or sub-acute stages of injury. Acutely, it may not be possible to safely implant an ESCS device. However, interventions in the sub-acute setting, before muscle atrophy has taken hold, may offer a more robust musculoskeletal environment for ESCS to function. Previous research has recognised that functional changes tend to occur earlier in the injury timeline, with the extent of motor improvements plateauing from 6 months onwards (Sumida et al., 2001; Waters, Yakura, Adkins, & Sie, 1992). Additionally, animal research has documented that early implementation of rehabilitation interventions improves recovery of function compared with delayed training (Brown, Woller, Moreno, Grau, & Hook, 2011; Norrie, Nevett-Duchcherer, & Gorassini, 2005). Hence, if the ideal study design were possible, based on the results of the current review, it would seem that ESCS applied to a large sample of participants classified as ASIA-C and

ASIA-D in the sub-acute setting may offer the greatest potential for significant motor recovery.

4.4. Quality appraisal

The relatively poor Downs and Black results reported in the current review can primarily be attributed to the inherent design limitations of the included studies (case studies and case series). The entirety of the studies in the current review fell into the poor category (score of < 14/28). The single participant studies of Ganley et al. (2005) and Harkema et al. (2011) shared the lowest score with 4/28. Conversely, the evaluation of upper limb function by Lu et al. (2016) scored highest with 13/28. The external validity, selection bias and power categories were identified as the poorest performers amongst most studies. Encouragingly, however, quality scores did trend higher chronologically, as sample size and methods improved. Further increases in study quality could be achieved in the future, with a few simple changes. Firstly, sufficient details of the training intervention along FITT principle (frequency, intensity, time, and type) and a reporting of study compliance could be expounded upon easily. Secondly, simple reporting of adverse events (whether they occurred or not). Thirdly, more robust statistical methods could be reported in greater detail. These adjustments in reporting would have significantly enhanced study quality across many of the included papers, with no change to either their methodology or sample size.

In order for ESCS to advance to the point of wide scale clinical acceptance as a therapeutic technology, higher level study designs are urgently required. RCT's may prove challenging for logistical and ethical reasons since finding a large number of participants at the same study site with suitably similar SCI's (and support infrastructure) is highly unlikely. Greater time and resources should therefore be expended on implementing multi-site studies to overcome these logistical constraints and greater transparency surrounding recruitment methods will also enhance the external validity of ESCS studies.

4.5. Reported outcome variables

Given the breadth of patient motor abilities reported in the current review, it is not surprising that a wide range of outcome measures were used to evaluate ESCS efficacy (Table 2). For the studies involving motor complete participants, the goal of training was largely to improve standing and basic

volitional movements. Therefore, the outcome measures utilised broadly reflected these goals. Time standing, level of physical assistance and percentage body weight support during standing were commonly used in such circumstances (Gill et al., 2018; Harkema et al., 2011; Rejc et al., 2015; Rejc et al., 2017a; Rejc et al., 2017b). A number of other studies with motor incomplete participants focused on gait related outcome measures such as gait velocity, distance achieved and the number of unassisted steps (Angeli et al., 2018; Carhart et al., 2004; Gorgey et al., 2020; Herman et al., 2002; Huang et al., 2006; Wagner et al., 2018). A modest selection of studies used established measures of muscle or joint force (Angeli et al., 2018; Angeli et al., 2014; Lu et al., 2016; Wagner et al., 2018). Regaining voluntary muscle force production forms the basis of motor recovery and so the omission of specific objective measurements of force by the majority of studies is notable. Likewise, muscle cross-sectional area is strongly correlated to force production (Jones, Bishop, Woods, & Green, 2008), yet only one study measured this variable preand post-intervention (Wagner et al., 2018). Previous reviews have highlighted the importance of selecting standardised and validated outcome measures to assess clinically meaningful changes in motor function for individuals with SCI (Alexander et al., 2009; Tomaschek, Gemperli, Rupp, Geng, & Scheel-Sailer, 2019). While one can sympathise with the difficulty of selecting appropriate outcome measures in the SCI/ESCS context, this review highlights the need for greater consistency between future studies, in order to allow a more formal synthesis of results at a later date.

4.6. Evidence of muscle activity

The most common outcome measure reported by almost all studies in the current review, was muscle activity via surface (and in some cases finewire) EMG. The reported methods were, in many cases, not reflective of best practice for recording (Hermens, Freriks, Disselhorst-Klug, & Rau, 2000), normalisation (Besomi et al., 2020) or presentation (Basmajian & De Luca, 1985) of dynamic EMG signals. A recent consensus statement on EMG signal normalization highlighted its importance for comparing muscle activity between measurement sessions and/or experimental conditions (Besomi et al., 2020). Amplitude normalisation procedures were not specified in 9 papers and in others are difficult to interpret. While lapses in methodological rigour may in part be

explained by the qualitative and descriptive nature of the EMG data presented, five studies did attempt to quantitatively evaluate changes in EMG, using inferential statistics. Again, the approaches utilised were in some cases questionable. Notably, Darrow et al. (2019) reported a significant change in the "rawnoise response magnitude", a novel EMG outcome variable, which appears to have originated with this group.

Several studies did present normalised EMG envelopes averaged across the gait cycle, providing a more comprehensive qualitative description of muscle activity with and without ESCS during assisted and unassisted stepping (Carhart et al.,2004; Ganley et al., 2005; Gill et al., 2018; Gorgey et al., 2020; Huang et al., 2006). Of note is the detailed qualitative description by Huang et al. (2006) of ESCS effects on muscle activity relative to the gait cycle and Gill et al. (2018) who quantitatively compared normalised EMG changes during discrete phases of the gait cycle. These highlights were arguably exceptions to the trends seen in the majority of studies. While presentation of exemplary un-normalized and un-rectified EMG traces does provide some qualitative evidence of motor engagement, it does little to move the field towards a consensus as to the efficacy of ESCS. Adherence to recommended recording, signal processing and normalization techniques would greatly improve the quality and consistency of this outcome measure in future ESCS studies.

4.7. Stimulation protocols used

Parameter details such as frequency, amplitude and placement of electrodes varied greatly between studies, and often only examples of selected parameters were provided. It must be appreciated that parameter selection and optimisation in practice is a constantly moving target. Daily ESCS training reported in Angeli et al. (2014) reduced the threshold intensity to produce force over the course of four months training, illustrating the need to adapt the stimulation parameters applied as the patient improves.

Similarly, there appears to be a task-specific nature to training. For instance, when the same parameters were applied to participants, minimal EMG activity was displayed in sitting but large amplitudes were generated in standing (Rejc et al., 2017a). Likewise, research reported by the same group observed that training with ESCS optimized for stepping subsequently impaired standing ability (Rejc et al., 2017a). Earlier work by Rejc et al. (2015) established that

parameters optimised for standing in one individual resulted in poor rhythmical EMG activity, insufficient to support standing, in another. This may be due to the distinct pathological fingerprint of each individual SCI and the co-existing interplay of propriospinal connectivity (Eisdorfer et al., 2020; Taccola et al., 2018).

In something as dynamic and reactive as ESCS, one can understand the difficulty of expressing real-time parameters in the static medium of a research paper. Authors such as Rejc et al. (2015) and Gill et al. (2018) should be commended for providing the location of each stimulator, stimulation configuration, frequency, and amplitude in graphic form. In future studies, further detailed descriptions are warranted concerning individual ranges, task specific parameters and how fatigue may affect parameter selection.

4.8. Limitations

In order to adequately interpret the summary findings presented, some limitations of the current review must be considered. Firstly, all data extracted was garnered through the texts themselves or the supplementary data available as an accompaniment. As the duration of many studies lasted years, it stands to reason that it would be difficult for the authors to relay every detail in publication form. Secondly, the current review focused exclusively on studies which evaluated ESCS for improving motor function in SCI. Consequently, a number of technical ESCS studies or other non-motor related studies; namely, studies examining autonomic function were not included. The combined therapeutic value of ESCS may therefore not have been fully evaluated. Finally, the authors acknowledge the logistical and technical constraints of conducting larger RCT studies of a surgically implanted device in such a diverse patient cohort. The current review therefore provides the best available evidence at the time of writing.

5. Conclusion

At present, there are very few options available to SCI individuals striving to recover sensory and motor function. Given the results of the current review, ESCS offers a promising avenue for further scientific exploration. While efficacy has yet to be fully established and at a large enough scale, four individuals in the current review did enhance their ASIA classi-

fication post-ESCS treatment. This at least indicates proof of concept and justifies further evaluation at greater scale. Future studies should aim to recruit larger cohorts to adequately evaluate ESCS, perhaps via the conduct of multi-site RCTs. Additionally, an attempt where possible to utilise homonymous, clinically acceptable outcome measures would greatly facilitate cross comparisons between studies. Finally, adherence to recommendations regarding recording and presentation of EMG signals would greatly enhance the quality of future studies and allow more meaningful interpretations by the wider clinical community.

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