NeuroMolecular Medicine (2020) 22:447–463
https://doi.org/10.1007/s12017-019-08589-9

REVIEW

A Review of Functional Electrical Stimulation Treatment in Spinal Cord Injury

Shiyu Luo[1] · Haonan Xu[2,4] · Yi Zuo[3,4] · Xiaogang Liu[5,6] · Angelo H. All[1]

Received: 27 August 2019 / Accepted: 28 December 2019 / Published online: 8 January 2020

Abstract
Functional electrical stimulation (FES) has been widely adopted to elicit muscle contraction in rehabilitation training after spinal cord injury (SCI). Conventional FES modalities include stimulations coupled with rowing, cycling, assisted walking and other derivatives. In this review, we studied thirteen clinical reports from the past 5 years and evaluated the effects of various FES aided rehabilitation plans on the functional recovery after SCI, highlighting upper and lower extremity strength, cardiopulmonary function, and balder control. We further explored potential mechanisms of FES using the Hebbian theory and lumbar locomotor central pattern generators. Overall, FES can be used to improve respiration, circulation, hand strength, mobility, and metabolism after SCI.

Keywords Spinal cord injury · Functional electrical stimulation · Rehabilitation · Neuroplasticity

Introduction

Spinal Cord Injury

In the United States alone, there are more than 250,000 people currently suffering from spinal cord injury (SCI), and over 17,000 new cases each year (National Spinal Cord Injury Statistical Center 2019; NINDS 2013). The majority of SCI cases result from traumatic events; vehicular accidents (39.3%) and falls (31.8%) are the most prevalent causes since 2015 (National Spinal Cord Injury Statistical Center 2019). About one-third of patients with SCI are re-hospitalized within the first year because of serious complications, including urinary, respiratory, neurological, cardio-circulatory, digestive, and musculoskeletal disorders (National Spinal Cord Injury Statistical Center 2019). Apart from physical impairments, SCI also poses severe financial burdens. Each year, medical expenses totaling $3 billion are spent on managing SCI; the individual cost can range from $370,000 to $1,130,000 for the first year of injury, and $40,000 to $190,000 for each subsequent year (National Spinal Cord Injury Statistical Center 2019; NINDS 2013).

In the case of contusion injury, a sudden mechanical force is imposed to the spinal cord, resulting in possible vertebrae fracture, spinal cord displacement, and definitely neuronal damage (NINDS 2013). This primary phase is followed by a secondary phase that is characterized by edema, hemorrhage, inflammation, and ischemic necrosis (Norenberg et al. 2004).

During the first 2 to 48 h post-primary injury, as a result of cellular metabolic and signaling dysregulation, the secondary damages start to compound relatively fast. Among them, the vasogenic and cytotoxic edema, inflammation, scarring and excess neurotransmitter release are the most common (Griffiths and Miller 1974; NINDS 2013). In

Shiyu Luo and Haonan Xu have contributed equally to this work.

✉ Xiaogang Liu
chmlx@nus.edu.sg

✉ Angelo H. All
hmn@jhu.edu

1 Department of Biomedical Engineering, Johns Hopkins University, Baltimore, MD, USA

2 Department of Chemical & Biomolecular Engineering, Johns Hopkins University, Baltimore, MD, USA

3 Department of Materials Science and Engineering, Johns Hopkins University, Baltimore, MD, USA

4 Institute for NanoBioTechnology, Johns Hopkins University, Baltimore, MD, USA

5 Department of Chemistry, National University of Singapore, Singapore, Singapore

6 The N.1 Institute for Health, National University of Singapore, Singapore, Singapore

vasogenic edema, the blood–brain-barrier is permeabilized, cerebral spinal fluid can leak into extracellular space, and cause swelling and pressure buildup. In cytotoxic edema, cellular dysregulation causes blood clogs, preventing normal oxygen and nutrient transport to the site of injury (Norenberg et al. 2004; Griffiths and Miller 1974; Tator and Koyanagi 1997). Moreover, astrocytes are recruited and become 'reactive' to form scars surrounding the injury site, which acts as a physical barrier to further resist oxygen transport and axon repair (NINDS 2013). The neutrophil influx and consequent inflammation also attribute to the cytotoxicity within the central nervous system (CNS) (Norenberg et al. 2004). Neuronal necrosis and oligodendrocyte apoptosis are exacerbated by axonal and myelin swelling, as well as excess neurotransmitters (NINDS 2013). These multifactorial secondary changes lead to significant altercations of micro-structures and microenvironment in the CNS parenchymal during the secondary phase of injury (Norenberg et al. 2004).

To address both primary and secondary injuries, a series of neuroprotective interventions and treatment strategies have been proposed. Common SCI treatment plan includes (i) stabilizing the spinal cord (Med 2008), (ii) re-establishing tissue hemodynamics (Furlan and Fehlings 2008), (iii) preventing exacerbation of inflammatory processes (Okada 2016), and (iv) inducing hypothermia (Loong et al. 2018; Maybhate et al. 2012). Depending on the severity of the injury, clinical outcomes of post-SCI treatments can vary. The severity of SCI is graded on the scale from A to according to the American Spinal Injury Association (ASIA) (Roberts et al. 2017), with Grade A indicating complete spinal cord injuries and Grade E signifying fully-restored sensorimotor functions. In brief, patients with Grade A SCI are completely paralyzed below the injury level with no sensorimotor function at the sacral segments. Grade B patients maintain some sensation, including at the sacral segments, but show no motor function. Grade C patients have some muscular function below the injury level but cannot necessarily move against bodyweight. Grade D patients have full sensory function, and at least half of essential muscular functions are maintained below the injury site; patients also have the ability to counteract gravity. Grade E patients have fully restored motor and sensory function but may suffer from neurologic phenomena such as abnormal reflexes (American Spinal Injury Association 2002).

Among SCI incidences since 2015, approximately 30% of injuries are complete, resulting in no function beyond the level of injury. About 60% of SCI cases are incomplete, where some levels of communication between the central and peripheral nervous system are maintained (National Spinal Cord Injury Statistical Center 2019). In the incomplete injury cases, there are spared fibers that are anatomically continuous through the injury site but do not constitute a part of responsive neuropathways (Bazley et al. 2011; Hansen et al. 2016). Hansen and colleagues demonstrated that spared axons could, at some point, exhibit plasticity in the extended neuronal network and take part in improving functional recovery (Bazley et al. 2011; Hansen et al. 2016). Hence, prevention of secondary injury and its complications that may further destroy spared fibers during the sub-acute phase can aid functional restorations post-injury, thereby improving the quality of life for SCI patients. FES has been shown not only to aid recovery in patients with incomplete SCI, but also to have beneficial effects on complete SCI patients, especially when it is administrated in combination with other treatments like rehabilitation and physical therapy.

Although adult CNS has negligible ability to regenerate, interventions such as stem cell replacement therapy have been shown to cause some degree of recovery in both complete and incomplete SCI rodent models (All et al. 2012; Bareyre et al. 2004). Somatosensory evoked potential (SSEP) monitoring is a noninvasive clinical tool used for assessing the injury onset, progress, and eventual recovery of the somatosensory pathways. SEEP is an electrical signal generated in response to external stimuli, it ascends through sensory pathways from periphery to the higher structures in the nervous system (Agrawal et al. 2008, 2010; Maybhate et al. 2012; Nuwer 1998). Due to this nature, SSEP is usually used to detect injury to the nervous system, as well as evaluating the neurophysiological changes during the recovery period (Al-Nashash et al. 2009; Mir et al. 2010, 2018). As detected by SSEP assessment, post-injury recovery is usually found to be associated with sprouting and rewiring of survived neurons after injury, a process generally referred to as neural reorganization (Bazley et al. 2011; Vipin et al. 2016). Typical sprouting process involves the formation of intra-spinal circuits near and around the lesion sites. Functional recovery could also be a result of neuroplasticity, which features compensational synaptic activities in surviving axons. It is perceivable that FES may also invoke neuroplasticity and play a critical role in network recovery and motor function improvements.

Functional Electrical Stimulation

FES is a procedure widely used in neurorehabilitation. Typical FES sessions involve electrical stimuli being applied to paralyzed nerve or muscle while a specific task such as cycling or rowing is being executed. (Martin et al. 2012; Ho et al. 2014; Peckham and Knutson 2005; Moe and Post 1962). It has been demonstrated that FES and other types of neuromuscular electrical stimulations can improve blood circulation, range of motion, muscle strength, and muscle spasticity (Martin et al. 2012; National Cancer Institute (n.d.)).

During FES sessions, electrical impulses are delivered to stimulate targeted nerves. Electrical stimuli could be applied at various locations, like neurons in the spinal cord, peripheral nerves, or surrounding skin above the muscles (Ho et al. 2014; Peckham and Knutson 2005). However, targeting nerves rather than muscle fibers is preferred because it allows for the application of much smaller charge densities, which requires less power, and consequently obtaining more effective outcome with less risks of tissue damage (Ragnarsson 2008; Gilman and Arbor 1983). Percutaneous systems use intramuscular electrodes that penetrate the skin barrier and are implanted into the muscles for directed activation. They allow repeatable and well-controlled contractions, even for the muscles in the deeper structures (Peckham and Knutson 2005). Despite their drawbacks of inevitable surgical procedures, higher cost, and additional risks such as infection, implantable FES electrodes are extremely effective and reliable with accurate configuring capabilities. In addition, implantable systems are more desirable for longitudinal studies and long-term applications. Various implantable systems are already available commercially, such as FreeHand (Fig. 1) (Hamid and Hayek 2008; Gater et al. 2011). In comparison, less invasive surface electrodes can be connected to an external stimulator worn around legs, arms or waists (Peckham and Knutson 2005). The surface systems are mostly noninvasive and the simplest to configure, but it is difficult to achieve accurate and effective stimulations with these types of systems.

Many research teams have evaluated the effects of FES for various tasks, including cycling (Ambrosini et al. 2010; Bellman et al. 2014), grasping (Kilgore et al. 2008), walking (Stein et al. 2010), stair climbing (Kobetic et al. 2009), and reaching (Ferrante et al. 2012). FES's role on strengthening muscles (Coupaud et al. 2008; Mangold et al. 2005), reducing pain (Koyuncu et al. 2010; Price and Pandyan 2000), enhancing circulation and blood flow (Thijssen et al. 2006; Van Duijnhoven et al. 2009), healing tissue (Itoh et al. 2008; Young et al. 2011), reducing spasticity (Sabut et al. 2011; Sahin et al. 2012), and retarding muscle atrophy (Gargiulo et al. 2011; Wahls et al. 2010) have also been investigated extensively. In addition to patients with SCI, FES can also be used for patients suffering from stroke, traumatic brain injury, and other neuromuscular diseases (Ho et al. 2014). FES has demonstrated promising potentials in improving qualities of life for patients with SCI. Further studies can help finetune the parameters of FES for various injury models and locations, as well as generate personalized treatment schedules to target individual rehabilitation goals.

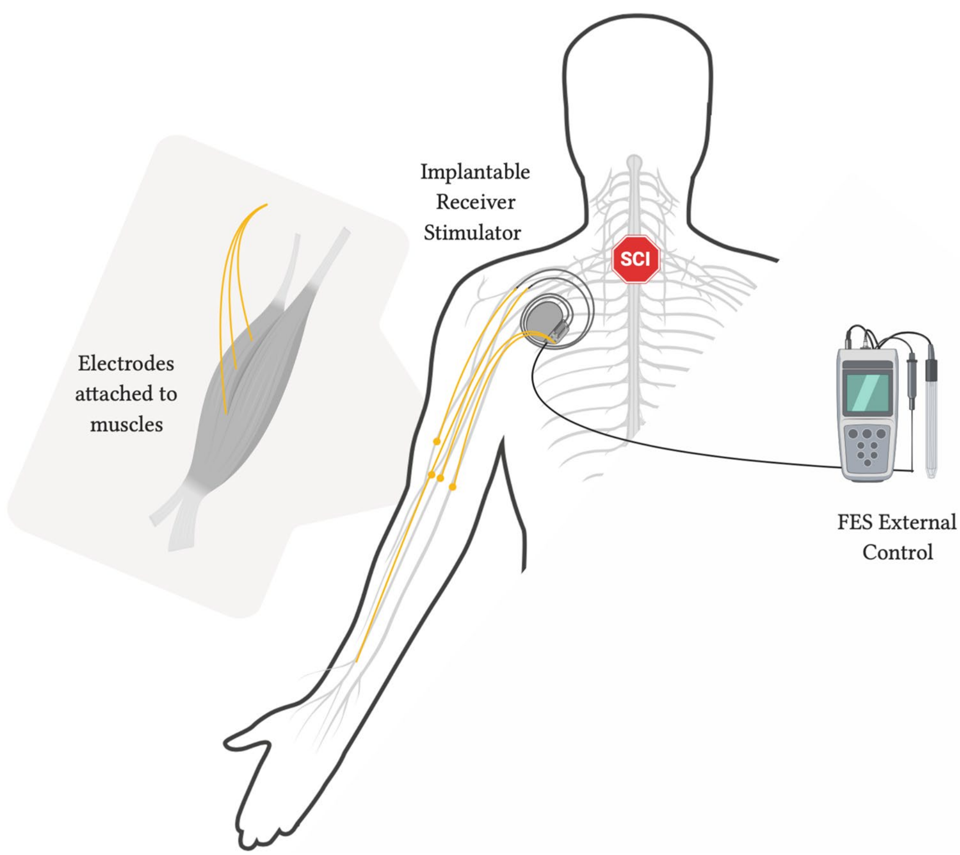

Fig. 1 Illustration of FES aided hand mobility system 'Free-Hand'. In functional electrical stimulation, electrodes can be attached to either muscles or nerves. Various FES aided motility systems are available commercially. In some systems, there can be an implanted component to FES, where the electrical stimulation is triggered by conduction coils connected to an external unit

Parameters of Functional Electrical Stimulation

Three parameters are used to describe electrical pulses: pulse width, frequency, and amplitude (Grill and Mortimer 1996; Thrasher et al. 2005; Eser et al. 2003; Kebaetse et al. 2002; Szecsi et al. 2007). Finetuning these parameters can optimize the effects of FES on evoking muscle contraction and reducing muscle fatigue, and they should be personalized based on patient's rehabilitation goals (Thrasher et al. 2005; Gorgey and Dudley 2008).

Pulses are usually delivered using sine wave, peak, or square patterns. The available pulse widths in FES devices are normally between 300 and 600 microsecond (μs) and variations in pulse width can have differing effects on the target muscle (Ibitoye et al. 2016). Researchers have found that low-frequency electrical stimulation with longer pulse width between 500 and 1000 μs can produce a lower level of muscle fatigue. Moreover, it has been also shown that shorter pulse width (10–50 μs) can potentially recruit more muscle fibers and generate larger joint torques in muscle fibers (Kralj and Bajd 1989; Grill and Mortimer 1996). Longer pulse width could also mean longer stimulus time in muscles with a higher number of nerve fiber depolarizations (Gorgey and Dudley 2008).

Stimulation frequency normally ranges between 20 and 50 Hz and could be adjusted depending on specific purposes of the treatments (Baker et al. 1988; de Kroon et al. 2005). Low-frequency FES is typically utilized to prevent muscle fatigue, and it can produce a smooth muscle contraction at lower force levels (Bhadra and Peckham 1997). When receiving higher frequency FES, patients can experience a smoother force response and a tingling feeling, which have been reported to be more comfortable (Sluka and Walsh 2003). It was also found that double frequency trains of 5 ms apart doublets separated by longer intervals could induce more fatigue resistance than square wave pulse constant-frequency trains (six stimuli, 200 μs of pulse width, separated by 70 ms) (Bickel et al. 2004; Ibitoye et al. 2016). Similarly, Deley et al. (2015) demonstrated that variable frequency train stimulation pattern could generate less fatiguing contractions. Modification of FES frequency trains can mediate muscle fatigue.

Amplitude describes the intensity of FES input; higher amplitude leads to a stronger depolarizing effect (Mesin et al. 2010). Typical values of stimulation amplitude are between 0 and 100 mA. The selection of the exact amplitude is often conducted on a per patient basis, and is influenced by the stimulation pattern, total stimulation time, and targeted region. Higher amplitude can increase the stimulation strength produced by FES and activate more muscle fibers (Doucet et al. 2012; Maffiuletti et al. 2002). However, recent studies suggested that excessive amplitude may limit the CNS signal input (Bergquist et al. 2011; Doucet et al. 2012). Researchers observed that lowering amplitude had no obvious effect on reducing fatigue. However, varying amplitude FES can generate more contractions than constant amplitude (Downey et al. 2011; Gorgey et al. 2009).

Materials and Methods

PubMed was used for primary searches of spinal cord injuries and functional electrical stimulations in the past 5 years. Among others, 13 peer-reviewed journals on FES with more than four clinical subjects per study were identified, reviewed, and reported. Studies with less than four subjects were excluded for lack of generality. Literature searches, article screening, and data summarization were completed by seven independent reviewers and compared for accuracy.

The majority of the literatures (Table 1) supports the conclusion that FES positively impact rehabilitation outcome. It is noteworthy that fatigue is the main adverse effect of FES, but it could be alleviated by using lower frequency and asynchronous stimulations.

Role of Functional Electrical Stimulation in Patients with Spinal Cord Injury

FES can either stimulate muscles to invoke specific action or support the rewiring and regeneration of damaged synaptic connections. It plays a prominent role in the rehabilitation process after SCI, mainly to improve and restore upper and lower limb functions, maintain cardiopulmonary health, and control bladder use. It has also been demonstrated that FES could help preserve bone mass, ease spasticity, reduce pressure ulcers, and control balance and posture. In this review, we focus on FES's roles in upper limb, lower limb, cardiopulmonary, and bladder functions.

FES and Upper Limb Functions

One of the most detrimental aspects of living with SCI is the loss of arm and hand functions. While surgical reconstruction has been used to improve upper limb performance, extensive motor training is needed for patients to re-learn the lost function (Bersch and Friden 2016). In the case of upper limb reconstructive surgery, FES could be used to strengthen the donor muscle after the transplant (Bersch and Friden 2016). Thorsen and colleagues have demonstrated that FES coupled with myoelectric control was able to improve the overall grasp strength of 24 patients, leading to the execution of new tasks in daily living (Thorsen et al. 2013).

According to holistic hand function tests, FES-assisted rehabilitation training improved hand function. However, increasing rehabilitation training intensity alone may not

Table 1 Primary studies included in this review

References	Sample size	Time since injury	Lesion site	ASIA classification
Bakkum et al. (2015)	20	≥ 8 years	C3–L2	A–D
Objective To compare the rehabilitation outcomes of handcycling combined with FES-assisted lower-extremity cycling versus handcycling alone for long-term SCI patients with low activity				
Methods During a 16-week controlled study, one group received both handcycle training and FES-assisted leg training and the other group received only handcycle training. The amplitude of FES was set at the highest value between 0 and 150 mA such that no discomfort to the patient nor excessive leg movement was caused. The stimulator used in this study had frequencies between 20 and 35 Hz and a constant pulse width of 400 µs				
Results Hybrid group had a decrease in submaximal VO_2 (mean oxygen consumption averaged over 30 s during submaximal exercise) compared to handcycle group. No other improvements from training were observed				
Conclusion Similar effects were witnessed for both hybrid cycling and handcycling. In this case, FES-assisted lower-extremity cycle brings no additional benefit				
Bersch and Friden (2016)	20	4–8 weeks	Mostly C4–C7	A–D
Objective To investigate the impact of preoperative and postoperative FES on reconstructive hand and arm surgery rehabilitation outcome				
Methods FES was used for the strengthening of the elbow extensor and the transferred muscle. All patients received FES during postoperative motor training. Two patients received stimulation to the donor muscles 3 months before surgery. The FES pulse width was set at 300 µs, frequency at 20 Hz. The amplitude of stimulation was chosen between 15 and 40 mA depending on the degree of the stimulation effect on adjacent muscles				
Results Preoperative donor muscle stimulation increased the strength of the donor muscles. Postoperative stimulation facilitated the activation of the transferred muscles. The improvements were observed clinically				
Conclusion FES has the potential of becoming a part of the hand reconstruction surgery procedure. It could be considered to assist pre-operative donor muscle strengthening as well as post-operative recipient muscle build-up				
Downey et al. (2014)	4	28–179 months	C4–T10	N/A
Objective To examine the effect of high and low frequency stimulation patterns on fatigue induced from neuromuscular electrical stimulation for asynchronous stimulation and conventional stimulation				
Methods 8 Hz and 16 Hz asynchronous, 32 and 64 Hz conventional neuromuscular electrical stimulations were adopted in leg-extension exercises in both healthy and SCI populations. Pulse width in this study is set constantly at 350 µs regardless of the stimulation pattern. The amplitude of the stimulation is adjusted before each trial to elicit the same preset initial torque and was kept below 100 mA				
Results The average time to fatigue of lower frequency stimulation is longer than that of higher frequency stimulation. Asynchronous stimulation also reduces fatigue comparing to conventional stimulation				
Conclusion Lower frequency and asynchronous stimulation pattern is advised in FES setting to reduce the fatigue side-effect of neuromuscular electrical stimulation				
Gorgey and Lawrence (2016)	10	> 12 months	C5–T10	A–B
Objective To explore the acute responses to FES lower-extremity training on cardiovascular functions				
Methods Patients with complete SCI participated in one session of FES-assisted lower-extremity training until exhaustion				
Results Cardiovascular and metabolic functions are improved in acute response to FES-assisted training, as suggested by the decreased ventilation-to-CO_2 ratio. FES-assisted training is found to be dependent on carbohydrate utilization but not fat utilization. There was a significant correlation between carbohydrate utilization and carbon dioxide production. The pulse width was set at 350 µs and frequency was at 33.3 Hz. The stimulation amplitude was set differently depending on the targeted region. The knee extensors and hamstrings received 140 mA stimulations while the gluteus maximus muscles received 100 mA stimulations				
Conclusion FES-assisted lower-extremity training brings an immediate decrease in ventilation-to-CO_2 ratio. The primary nutrient utilized is carbohydrate				
Gorgey et al. (2017)	9	> 2 years	C8–T10	A
Objective To compare the effects of arm cycling and FES-assisted lower-extremity cycling on muscle improvement				
Methods One group received FES-assisted cycling while the other group received upper-body ergometer training. Muscle biopsies were performed to examine gene expressions. The stimulation amplitude was set at 140 mA and frequency was 60 Hz				

Table 1 (continued)

References	Sample size	Time since injury	Lesion site	ASIA classification
Results The metabolically active genes GLUT-4 (glucose transporter-4), AMPK (adenosine monophosphate kinase), and PGC-1α (PPAR coactivator 1 alpha) were found to increase in vastus lateralis after FES-cycling as well as in triceps after upper-body ergometer training. Enhanced expressions of these genes suggest increased metabolism and lowered insulin resistance risk				
Conclusion FES-training can upregulate metabolically active genes in paralyzed muscles, comparable to the effect of exercise on heathy muscles				
Kapadia et al. (2014b)	27	< 6 months	C3–C7	Traumatic incomplete sub-acute SCI
Objective To compare the effectiveness of single dose and double doses of conventional occupational therapy (COT) to those combined with FES				
Methods 45 h and 80 h of COT therapy were given to two COT groups respectively. Another group received FES training for 40 h, then COT therapy for 40 h. FES training involves electrical stimulation to hand and wrist during daily living activities training. The FES group received biphasic electrical stimulation with 250 µs pulse width and 40 Hz frequency. The amplitude of the stimulation varied between 8 and 50 mA, with typical values ranging between 15 and 30 Hz				
Results The FES + COT group saw more improvements in functional measure score and spinal cord independence score; the two COT groups had similar improvements				
Conclusion The study reports better recovery outcomes for a combination treatment of COT and FES than COT treatment alone. The increase in COT intensity alone does not yield better results				
Kapadia et al. (2014a)	34	≥ 18 weeks	C2–T12	C–D
Objective To compare the effectiveness of FES-assisted lower-extremity training and traditional training for chronic SCI patients				
Methods For 16 weeks at three sessions per week, the test group received FES-assisted walking training on a treadmill, the control group received traditional aerobatic and resistance training. The test group received electrical stimulation with 40 Hz frequency. The amplitude and the pulse width were set differently depending on the patient needs and muscles stimulated. The amplitude ranged from 8 to 125 mA and pulse width ranged from 0 to 300 µs				
Results In FES-assisted walking group, spinal cord independence measure (SCIM) mobility sub-score increased compared with the control group. Other subs-cores had similar improvements in both groups				
Conclusion No definitive conclusion can be drawn on the benefits of FES-assisted training over aerobatic and resistance training. Both modalities demonstrated significant improvements to walking ability among incomplete SCI patients				
Menendez et al. (2016)	10	4–29 years	C6–L1	n/a
Objective To explore the acute effects of whole-body vibration (WBV) and electrical stimulation (ES) on blood circulation and skin temperature				
Methods All patients underwent a five-session protocol as follow; habituation, WBV alone, ES alone, simultaneous WBV with ES, and 30 s of ES following 30 s of WBV. Rectangular and biphasic electrical stimulations with pulse width of 400 µs and frequency of 8 Hz were applied to the ES group. The amplitude of the stimulation was determined in the first session for each subject to match their motor threshold and was maintained in the subsequent sessions				
Results All treatments improved patient's circulation as measured by their mean and peak blood velocity. The simultaneous WBV and ES treatment lead to the most improvements				
Conclusion The simultaneous WBV and ES can be used to improve circulatory health for SCI patients				
Ojha et al. (2015)	15	4–35 months	C6–L3	A–D
Objective To analyze the effectiveness of surface electrical stimulation on reducing detrusor over-activity				
Methods One group received electrical stimulation on the posterior tibial nerve (PTN) while the other one received stimulation on the penile nerve (DPN) to facilitate bladder voiding. The stimulations were given with 200 µs pulse width and 20 Hz frequency. The amplitude of the rectangular pulses was set between 10 and 40 mA				
Results Voiding chart showed statistically significant improvements for PTN stimulation. No significant differences were observed in the cystometrogram data for either group				
Conclusion PTN and DPN stimulation effects cannot be conclusively determined. Further study is needed				
Petrie et al. (2015)	12	chronic (> 1 year)	C4–T10	A

Table 1 (continued)

References	Sample size	Time since injury	Lesion site	ASIA classification
Objective To compare the rehabilitation outcome between two stimulation frequencies (5 Hz and 20 Hz) for patients with complete chronic SCI				
Methods Twitch force was assessed before and after a single session of electrical stimulation was administered to two separate groups of patients at 5 Hz and 20 Hz. The pulse width was maintained at 200 µs. The stimulus amplitude was adjusted for each patient with a maximal amplitude determined at the start of the trial. The amplitude did not exceed 300 mA. Bilateral percutaneous muscle biopsies were performed on a subset of subjects. RNA was subsequently extracted and analyzed				
Results Both 5 Hz and 20 Hz stimulations resulted in a similar degree of fatigue. However, 5 Hz stimulation group demonstrated a larger increase in key metabolic transcription factors				
Conclusion Low-frequency muscle force training for patients with SCI still leads to fatigue. However, significant upregulation of metabolically active genes such as PGC-1α was seen in 5 Hz group when compared to the 20 Hz group				
Thorsen et al. (2013)	27	> 6 months	C5–C7	A–C
Objective To study the application of myoelectrically controlled functional electrical stimulation (MeCFES) on improving overall hand grasp strength				
Methods Patients participated in activities of daily living training assisted with MeCFES for twelve two-hour sessions. The MeCFES system delivered biphasic electrical stimulation with 300 µs pulse width and 16 Hz frequency. The stimulation amplitude was adjusted automatically according to myoelectrical recordings and had a maximum limit				
Results FES coupled with myoelectric control was able to improve the overall grasp strength of 24 patients, leading to the execution of new tasks required in daily living				
Conclusion As a noninvasive neuroprosthesis, MeCFES provides a safe rehabilitation modality for improving post-SCI hand function				
Wilbanks et al. (2016)	10	4–32 years	T4–T12	A–C
Objective To evaluate the effects of FES-assisted rowing on aerobatic fitness and pain relief				
Methods FES-assisted knee extension and flexion during a 6-week training at three sessions per week and 30 min per session. Qualitative assessment and exercise performance were recorded before and after the training period. The stimulation amplitude was adjusted between 0 and 100 mA				
Results A post-training increase of VO2 peak was observed. VO2 peak measures the maximum amount of oxygen a person can utilize during intense exercise. Shoulder pain relief was also reported as a result of FES rowing				
Conclusion The reported increase of VO2 peak demonstrates the positive impact of FES-assisted training on aerobic fitness. The pain alleviation of FES rowing is also an important advantage				
Yasar et al. (2015)	10	> 24 months	C4–T12	C–D
Objective To assess the benefits of FES aided cycling on functional improvements for chronic SCI patients				
Methods Patients with chronic SCI participated in three times per week FES-assisted stationary bike training for 16 weeks with 1-h session each. FES amplitude was set between 10 and 140 mA, pulse width 250 µs, and frequency at 20 Hz				
Results FES-cycling led to significant improvements in motor score and functional independence measure, although no significant improvement in gait control was detected				
Conclusion FES-cycling is shown to be beneficial in decreasing muscle spasticity and improving functional recovery for SCI patients				

yield positive results or bring greater benefits (Kapadia et al. 2014b). Kapadia and colleagues compared the rehabilitation outcome of patients who receive conventional occupational therapy (COT) alone versus patients who also receive FES therapy. COT is a form of highly individualized rehabilitation therapy consists of muscle strength training, stretching, and practicing of activities of daily living (ADLs). Certified COT therapists would customize the training schedule based on the overall conditions of the patients. For patients who receive FES in their study, electrical stimulation was given to wrist flexors and extensors, finger flexors and extensors, as well as thumb oppositions during their performance of ADLs (Kapadia et al. 2014b). The study reports better recovery outcomes for patients who received a combination of COT and FES than the COT-only group (Kapadia et al. 2014b). This result demonstrates the clear benefits of FES in upper limb functional recovery after SCI.

FES and Lower Limb Functions

As a primary focus of FES-assisted rehabilitation, lower limb functional recovery through FES has attracted consistent research interest. During FES-assisted exercise, muscles such as quadriceps, hamstrings, and gluteal muscles are the usual stimulation targets. A prospective single-arm study involving stationary FES cycling (RT 300-SLSA; Restorative Therapies, Baltimore, MD, USA) was conducted over 16 weekly treatment sessions with chronic SCI patients (Yasar et al. 2015). Functional Independence Measure (FIM) score containing 18 measures of physical, psychological, and social function was used as the main parameter for assessing SCI severity and recovery progress (Yasar et al. 2015). Total motor score, gait stability, and oxygen consumption rate while walking were also evaluated at 3-month intervals. This study concluded that FES-cycling led to significant improvements in the motor score and FIM score, although no significant improvement in gait control was detected. Furthermore, FES-cycling was shown to be associated with a decrease in muscle spasticity (Yasar et al. 2015). The findings of this study positions FES-cycling as an alternative to the conventional rehabilitation training plan. Further studies with a well-defined control group may help eliminate the concerns of cycling alone being the source of improvement (Yasar et al. 2015).

In a randomized crossover study, Menendez et al. investigated the effectiveness of FES combined with other means of stimulation. The effects of isolated, simultaneous, and consecutive applications of whole body vibration (WBV) at 10 Hz and electrical stimulation (ES) were tested. All patients underwent a five-session protocol consisting habituation, WBV alone, ES alone, combined WBV with ES, and 30 s WBV then 30 s ES. Each training module contained ten sets of one-minute intervention followed by one minute of rest. Measurements of the skin temperature as well as the mean (MBV) and peak blood velocity (PBV) of the popliteal artery were recorded both before and five minutes after the completion of each module. The study found that all stimulation regimens increased the mean and peak blood velocity when compared to the baseline measurements. However, the simultaneous WBV and ES showed the greatest MBV and PBV increase. Furthermore, treatment of WBV in conjunction with ES also resulted in the earliest and highest increase in calf skin temperature (Menendez et al. 2016).

Kapadia and Masani et al. reported a randomized parallel-group trial with 27 subjects who had sustained chronic incomplete SCI between C2 and T12, ranging from class C or D on the ASIA scale. The control group received tailored resistance and aerobic training; the intervention group received FES stimulation to bilateral quadriceps, hamstrings, dorsiflexors, and plantar flexors using two four-channel electric stimulators while undergoing body weight support treadmill training. Both groups maintained the same volume of therapy across a 16-week period and were assessed at the baseline, 4-month, 6-month, and 12-month period. Measurements of gait, balance, spasticity, Spinal Cord Independence Measure (SCIM), SCIM mobility sub-score, and FIM locomotor score were collected. SCIM score is a 100-point scoring system assessing four subcategories: self-care, respiration, sphincter control, and mobility. The results showed that SCIM mobility sub-score had improved for the FES group. Other measurements of the test group are not significantly different from control. It suggested that both FES-assisted treadmill training and resistance/aerobic training improve walking for chronic incomplete SCI patients. The enhanced SCIM mobility sub-score warrants further investigation on FES-assisted walking (Kapadia et al. 2014a).

FES and Cardiopulmonary Functions

Due to the physical impairment and mental distress associated with SCI, patients often report reduced participation in physical activities and deteriorating aerobic fitness. In addition, the loss of innervated skeletal muscle could further restrict respiration during exercise. The chronic inactivity can impair cardiopulmonary functions in SCI patients, leading to potentially serious cardiovascular disease (CVD) (Figoni 1990). For patients with cervical and high thoracic SCI, cardiovascular malfunctions due to deregulated sympathetic flow could also occur if supra-spinal vasomotor pathways are disrupted (Partida et al. 2016).

FES-assisted training has been shown to positively impact the cardiovascular functions of SCI patients, primarily by increasing exercise and peak ventilation (Wheeler et al. 2002). Gorgey et al. studied the effects of FES-cycling on SCI patients by monitoring their ventilation, carbon dioxide production, ventilation-to-carbon dioxide ratio, and substrate utilization. Although they saw a large increase in ventilation and decrease in ventilation-to-carbon dioxide ratio after FES-cycling, further examinations are needed to correlate these changes to cardiovascular health (Gorgey and Lawrence 2016). Another report by Wilbanks and colleagues examined FES-rowing training using a commercially available rowing machine (Concept 2™ Dynamic Indoor Rower) adapted to allow FES-assisted knee extension and flexion. After a 6-week training, they reported a post-training increase of VO2 peak, which is a measurement of the maximum amount of oxygen a person can utilize during intense exercise. This report of VO2 peak demonstrated desirable impacts of FES-assisted training on aerobic fitness (Wilbanks et al. 2016).

In summary, FES shows promising results on the cardiovascular health of SCI patients, especially on improving the peak ventilation. Further investigations are needed to verify how the improvement on peak ventilation is associated with cardiovascular health.

FES and Bladder Functions

Post-SCI bladder dysfunction is often attributed to neuronal disconnection between lower motor neurons, external sphincter and pelvic floor, as well as dysfunction of the pelvic preganglionic parasympathetic neurons that innervate bladder (Creasey and Craggs 2012). Immediately following SCI, micturition reflexes, or bladder contractions that maintain urine flow for complete voiding are disrupted, resulting in possible lower urinary tract sphincter dyssynergia (uncoordinated and abrupt muscle movements) and hyperreflexia (over-responsive reflexes). The failure to control bladder volitionally would impair bladder voiding and cause high-pressure buildup. If left untreated, it could cause renal failure. Furthermore, urinary tract infection (UTI) is the most common infections among SCI patients, which can lead to life-threatening dysreflexia (Salameh et al. 2015).

In a pilot study on SCI patients with detrusor over-activity, Ojha et al. showed improvement of bladder function based on voiding charts following posterior tibial nerve (PTN) stimulation (20 Hz, 10–40 mA electrical stimulation for 20 min/session/day for 14 consecutive days) (Ojha et al. 2015). The same stimulation over dorsal penile nerve (DPN) also showed a potential trend for positive outcome, despite no statistically significant differences were recorded. Cystometrogram (CMG) readout suggested there were no significant improvements for either stimulations. CMG is a bladder function assessment procedure used to measure bladder pressure, urine volume, and bladder neck function. The authors suggested that the lack of improvement on CMG reading could be affected by the underlying UTI or autonomic dysfunction, and further studies on long-term stimulation effects are needed.

Following SCI, urinary tract infection and bladder dysfunction are often attributed to the disruption of micturition reflex and renal insufficiency, which ultimately culminates in renal failure. The sacral root contains bladder motor efferent, and its stimulation has been shown to reliably maintain bladder function in the primate model (Brindley 1977). Such a stimulating device could be implanted over the sacral anterior root of the spinal cord in order to deliver electrical stimulation. The stimulation frequency was set to 15 pulses/second which was determined as the optimal setting, and the stimulus voltage was set at the maximum stimulus where all parasympathetic fibers are activated with no substantial benefits upon further voltage increase. When tested in the baboon, an external transmitter could facilitate the emptying of the bladder on demand. The strong electrical stimulus would contract bladder smoothly; when paired with a two-second gap between stimulus, the striated muscles relax during the gaps, thus allowing bladder voiding. Nonetheless, the sacral root stimulation system is an invasive procedure and is accompanied by irreversible posterior rhizotomy and removal of the remaining sensory reflexes, which poses deserved safety concerns in patients with incomplete SCI. Furthermore, McCoin and colleagues attempted to suppress urethral sphincter reflexes in felines with patterned surface stimulation of sacral dermatomes. Adult male cats, which underwent spinal transection, were implanted with bilateral extradural sacral root electrodes to facilitate bladder control. They demonstrated that sacral root stimulation (0.75 s on, 0.25 s off, 20 Hz stimulation frequency) could reduce abnormal urethral reflex (McCoin et al. 2013).

Despite the success of sacral root stimulation in animal studies, further investigations are needed for clinically applicable non-invasive FES systems, with special considerations on safety, feasibility and efficacy.

Molecular Mechanisms

Hebbian Theory and Central Pattern Generator

Numerous clinical reports have shown how FES may benefit the patients suffering from SCI, both through the direct effects of preventing the prolonged neuromuscular loss, and the secondary effects of maintaining cardiopulmonary health. However, little is reported about the underlying physiological and molecular mechanisms. In this context, two theories that are widely recognized are the Hebbian theory of synaptic plasticity and the role of mammalian central pattern generator (CPG).

The Hebbian theory was first postulated in 1949 by Donald Hebb. His attempt at explaining synaptic plasticity is now popularized as the simple phrase "neurons that fire together, wire together" (Hebb 1949). To elaborate, the synaptic connection towards a target neuron can be enhanced if the activation of a target neuron is closely timed (Young 2015). In the context of spinal cord injury, at least three scenarios have been proposed where Hebbian learning may explain the positive effects of FES (Fig. 2). First, FES can guide the adaptive plasticity. After SCI, the CNS plasticity increases, as indicated by the reorganization of the neuron networks. However, not all plasticity is beneficial for recovering sensorimotor function; uncontrolled plasticity may induce maladaptive reorganization. Passive muscle activation through FES can be an effective method to guide adaptive plasticity (Ethier et al. 2015; Moxon et al. 2014; Dancause and Nudo 2011). Second, FES reactivates the neurons damaged by SCI. Since passive movements of the wrist and ankle share the same nodes of the cortical motor network as that of physiological movement, FES could potentially activate the sensorimotor neurons within the spared neuropathways around the epicenter of injury and surrounding area when they share the same connections towards target neuron (Carel et al. 2000; Dobkin 2003).

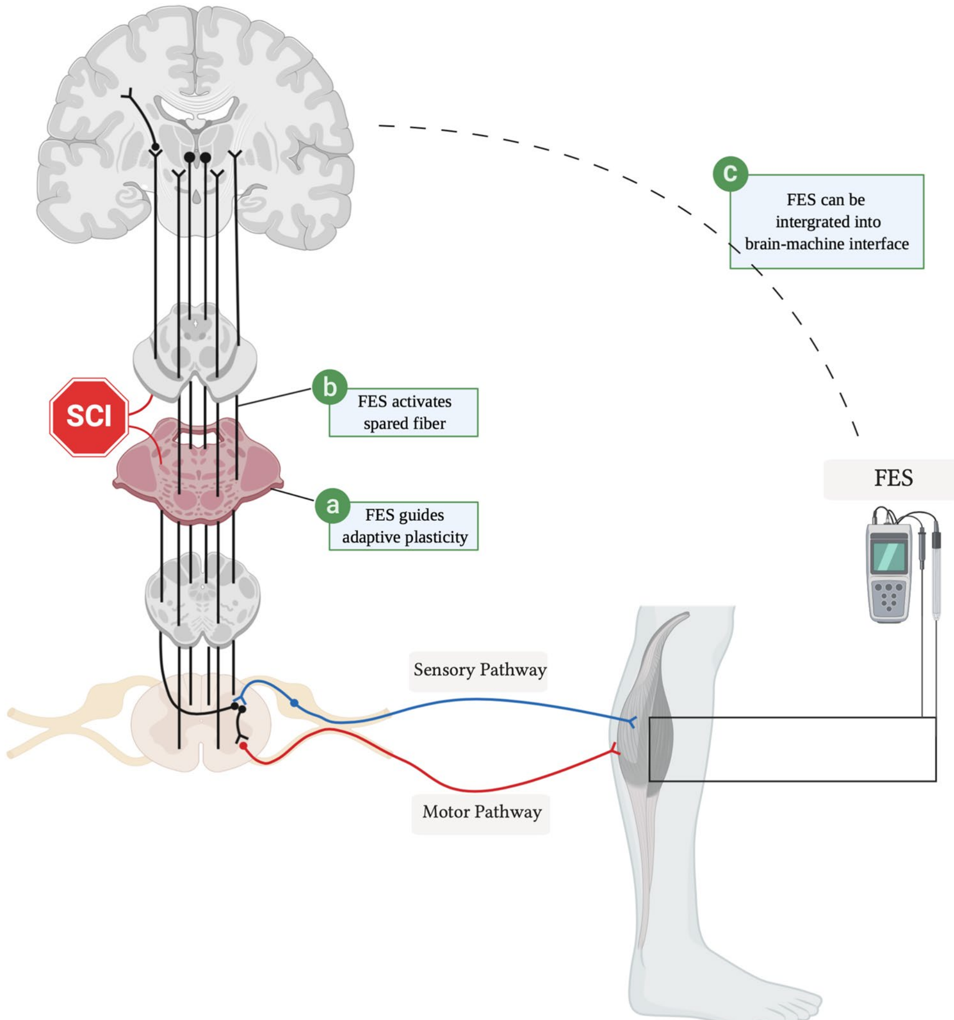

Fig. 2 Functional electrical stimulation as explained by Hebbian theory. After SCI, damaged ascending and descending neuropathways continue to waste away, which lead to paretic and paralyzed muscles. FES can be used to strengthen the functional links between the brain's connections and affected muscles by guiding adaptive plasticity, activating damaged network via spared fiber, and inducing neuronal plasticity via cortical neuron controlled FES (sensory pathways are shown in blue, and motor pathways are shown in red)

Third, recent animal studies have shown promises for using brain–machine interface to control the signals for FES. As a result, brain-controlled FES could be used to increase the connection between the brain and paretic muscle by inducing neuronal plasticity (Ethier et al. 2015; Moritz et al. 2008).

In the case of FES-aided hand systems, by applying electrical stimulation at the same time as the patient was trying to flex hand or arm muscles, ascending motor pathway would be activated, thus enhancing synaptic connections of regenerated axons. The locomotor training could also facilitate the regeneration and rewiring of appropriate interneurons and motoneurons. Furthermore, long-term improvements post FES is also possible, mainly due to the consolidation and facilitation of synaptic formations after axons have been regenerated (Young 2015).

Another theory is about the role of Central pattern generators (CPGs). CPGs are neuronal circuits that respond to chemical (i.e. neurotransmitters) and electrical signals (i.e. FES) for producing rhythmic motor outcomes (Young 2015; Marder and Bucher 2001). Locomotor CPG within the lumbar spinal cord L2 controls the hip, knee, and foot muscles. Because of CPG and its subsequent input, lower limb motor functions can be initiated at the CPG without brain directly activating motoneurons (Young 2015; Grillner and Wallen 1985). Cerebellum processes CPG motor commends and stepping signals transmitted through the spinocerebellar track, and initiate corrective motor cues via vestibulospinal, rubrospinal, and reticulospinal tracks. In the case of dysfunctional cerebellum or damaged spinocerebellar pathway, locomotor perturbation cannot be addressed but CPG commands can still be relayed to motoneurons if downstream pathways are intact (Fig. 3). In addition, brainstem may also contributes to the input of CPG, as suggested by elicited walking in decerebrate primates (Grillner and Wallen 1985). While it has been challenging to exam human CPG's role in locomotion, Dimitrijevic et al. have demonstrated epidural electrical stimulation was able to generate step-like movements in chronic complete SCI patients (Dimitrijevic et al. 1998; Guertin 2012). During the study, 25–60 Hz and 5–9 V of non-patterned electrical stimulus was delivered to

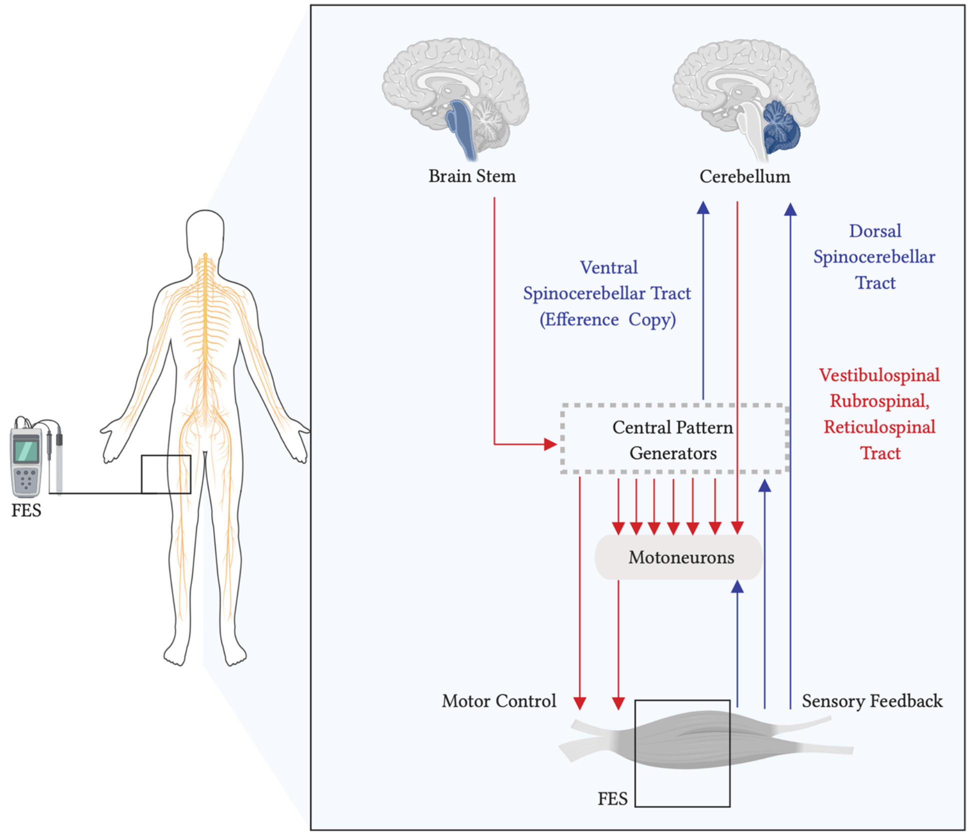

Fig. 3 Functional electrical stimulation as explained by central pattern generators. CPG can invoke locomotion of lower limb without the input from the brain, which makes it a great therapeutic target. Even when a patient suffers from complete SCI, epidural stimulation to the CPG leads to step-like rhythmic motion. FES is hypothesized to activate CPG locomotor center as well (sensory pathways are shown in blue, and motor pathways are shown in red)

six subjects with complete SCI at thoracic cord level T10 through sacral cord S1, and stimulus of 5–9 V, 0.2–0.5 ms width, and 25–50 Hz to the posterior of L2 segment elicited rhythmic step-like EMG response with lower limb flexion/extension (Dimitrijevic et al. 1998). Furthermore, it was suggested that CPGs are particularly susceptible to Hebbian type learning (Righetti et al. 2006; Young 2015). It is perceivable that FES can strengthen the neural connections between lower limbs and CPG, and elicit locomotion without direct input from the brain (Fig. 3) (Marder and Bucher 2001; Rossignol 2000).

Muscle Conversion and Gene Expression

In contrast to the imperceptible theory of Hebb's postulate and CPG, FES also leads to measurable changes in muscle fiber and its gene expression. There are two main categories of skeletal muscle fibers: slow-twitch (type I, red, aerobic) fiber and fast-twitch (type II, white, anaerobic) fiber (Mohr et al. 1997; Ragnarsson 2008; Fazio 2014). After SCI, prolonged paralysis and inactivity can transform slow-twitch muscle into fast-twitch muscle with additional muscular atrophy. As a result, the muscle becomes highly fatigable when stimulated. Although FES cannot prevent neurological loss following SCI, it can facilitate the conversion of fast-twitch fibers back to slow-twitch fibers (Mohr et al. 1997; Ragnarsson 2008; Peckham and Knutson 2005; Fazio 2014). As early as 1997, Mohr et al. has studied the effect of FES aided cycling with 10 chronic SCI patients, 6 tetraplegic and 4 paraplegic patients. All patients received electrical stimuli on the skin over the motor points of gluteal, hamstring, and quadriceps muscles, and they were exercise-trained on computerized feedback-controlled cycle ergometer. Each muscle had two electrodes, a total current of 18–40 mA depending on muscle type, and a maximum of 130 mA for safety; each electrode had six channels, with 30 Hz, 350 ms rectangular pulse per channel (Mohr et al. 1997; Kjaer et al. 1994). After a 1-year-long, three times per week, 30 min per session training, all of the patients showed improved endurance, exercise energy output, and oxygen uptake. Moreover, MRI images revealed an average of 12% increase in thigh muscle mass. Biopsies showed that fast fatigable type IIB fiber reduced from 63 to 32%, fatigue-resistant type IIA fiber increased from 33 to 61%, and slow-twitch type I fiber increased from less than 5% to 7% of the total (Mohr et al. 1997). In addition to the muscle fiber composition changes, the enzymatic activity of citrate synthase was also doubled. Being a key member of the Krebs cycle, increase in citrate synthase activity is indicative of mitochondrial oxidative process, presumably utilized for the aerobic metabolism of type I slow-twitch fiber (Mohr et al. 1997).

In a similar study of FES cycling involving 18 patients with complete and incomplete chronic SCI, Griffin and colleagues have demonstrated that FES cycling can also improve glucose metabolism (Griffin et al. 2009). Besides muscular atrophy and fiber conversion, inactivity after SCI could lead to increasing cholesterol, obesity, and diabetes mellitus as well (Ragnarsson 2008). Reduced oral glucose tolerance and insulin-mediated glucose uptake are both risk factors for type II diabetes (Yarar-Fisher et al. 2013; Griffin et al. 2009). After 10 weeks of FES cycling with three sessions per week, and 30 min per session, Griffin's patients had significant improvements in glucose tolerance. Importantly, a panel of inflammatory makers of CRP, IL-6, and TNF-a had a significant reduction in expression as a results of FES cycling. High level of serum TNF-a has also been associated with insulin resistance and type 2 diabetes. It was demonstrated that FES cycling could reduce TNF-a and lower this risk factor (Griffin et al. 2009). A separate study also looked at the protein expression of glucose transporter-4 [GLUT-4] and adenosine monophosphate kinase [AMPK] as results of FES cycling (Gorgey et al. 2017). GLUT-4 is key member of glucose utilization pathways. When compared to healthy subjects SCI patients have lower GLUT-4 baseline, and its upregulation could reduce glucose intolerance (Yarar-Fisher et al. 2013). Yarar-Fisher and colleagues have shown that there is increased phosphorylation of signaling proteins in compensation of reduced GLUT-4 in SCI patients, one of which is AMPK. AMPK is a transcriptional coactivator involved in glucose and fatty acid uptake, as well as mitochondrial biogenesis. After 16 weeks of five sessions per week training, GLUT-4 was upregulated by 3.8 folds and AMPK was upregulated by 3.4 folds (Gorgey et al. 2017). Based on the biopsy proteomic results, FES cycling can modulate gene expression in paralyzed muscle comparable to that of innervated muscle (Gorgey et al. 2017).

Further Improvements

Muscle fatigue is a common symptom among SCI patients undergoing FES treatments. It is defined as lower than the normal ability to generate force or a reduction in peak force upon exercise (Gorgey et al. 2009; Wan et al. 2017). Physiological muscle force generation includes excitation of cortices, stimulation of motor unit, activation and contraction coupling resulting in muscle activation (Wan et al. 2017). FES is an effective way for passive muscle recruitment, and because of how it is opposite to that of physiological recruitment, muscle fatigue could occur. Since fast-twitch fibers are innervated by larger diameter axons, they couple more with the electrical field during FES, and are activated before slow-twitch fibers (Robinson 2008; Lynch and Popovic 2008). Fast-twitch fibers are more prone to fatigue; hence it is common to observe fatigue during FES.

Muscle fatigue may also be caused by the failure of neuromuscular transmission, deficiency in metabolic support needed for contraction, as well as excitation–contraction coupling failure (Sieck and Mantilla 2004). Neurotransmitters, blood calcium level, temperature, blood flow, oxygenation, and overall energy supply, can all interfere with physiological force generation and result in muscle fatigue (Wan et al. 2017). The neurotransmitters such as serotonin, dopamine, and noradrenaline are utilized by CNS to stimulate motoneurons and generate muscle force. Weakened calcium release from the sarcoplasmic reticulum (SR) causes skeletal muscle fatigue (Wan et al. 2017). Healthy blood circulation delivers oxygen and removes metabolic byproducts, it has an indispensable role in force production (Wan et al. 2017). Adenosine triphosphate (ATP) is converted from stored glycogens and serves as a major energy carrier molecule used to sustain muscle contraction (Wan et al. 2017). Other metabolites such as hydrogen ions, lactate, reactive oxygen species, inorganic phosphate, cortisol, catecholamine, shock protein, and orosomucoid all have important roles in muscle function and muscle fatigue (Wan et al. 2017). Despite having three main groups of biomarkers for muscle fatigue: ATP metabolism, inflammatory, and oxidative stress, no effective treatments have been developed or recommended for muscle fatigue yet (Wan et al. 2017).

When fixed-parameter stimulations are used to stimulate the same motor units repeatedly, the metabolic factors, motor unit recruitments, and muscular contractions all increase, which can contribute to muscle fatigue (Gorgey et al. 2009). Two major types of FES-induced muscle fatigue have been reported, high and low-frequency fatigues (Bersch and Friden 2016). High-frequency fatigue occurs at ≥ 50 Hz, which causes neurotransmitters to remain in the activated state. In contrast, low-frequency fatigue occurs from 15 to 50 Hz, which decouples the neurological excitation and muscular contraction (Bersch and Friden 2016). Nonetheless, the fatigue could be reduced by adjusting and customizing the associated stimulation parameters of FES (de Kroon et al. 2005; Doucet et al. 2012; Gorgey et al. 2009; Thrasher et al. 2005). Notably, Downey and colleagues have shown that ultra-low frequency multi-channel stimulation at 8 Hz has significant fatigue reduction effects (Downey et al. 2014). This suppressed frequency was able to stimulate motor unit because the electrical pulses are delivered asynchronously to different muscles within a single motor unit, leading to a high composite stimulatory effect (Downey et al. 2014). Optimizing rehabilitation exercise, stimulation electrode positioning, and feedback control are also proposed as methods to reduce fatigue from FES (Ibitoye et al. 2016).

While a variety of reasons can contribute to muscle fatigue, FES can be optimized to minimize this shortcoming through the adjustment of stimulation parameters and rehabilitation schedule. Further studies would help to fine-tune the balance between intensive rehabilitation needs and physical limits of the muscle.

Discussion

As previously mentioned, FES has been used in a wide range of rehabilitation regimens. It can have both direct effects such as facilitate walking, improve griping, and indirect effect like maintaining cardiovascular health. Both complete and incomplete SCI patients responded to various FES training plans. It is also important to note that conflicting results were also documented. Ralston and colleagues have observed no immediate improvements on urine output, lower limb swelling, or spasticity from FES aided cycling of 14 participants over a 2-week period (Ralston et al. 2013). Currently, it is unclear the reason behind these conflicting reports. However, personalized medicine, finetuning training schedule and stimulation parameters to individual patient needs, as well as increasing sample size, and conduct multicenter studies may provide more insights into the specific efficacies of FES treatments. Furthermore, adjusting specific FES parameters such as stimulation frequency, target muscle, treatment schedule plays a prevalent role in training outcome. Etiologically speaking, FES has been proposed to guide adaptive plasticity, activate spared fibers, and stimulate central pattern generators while bypassing SCI damaged pathways. Our own in vitro research further suggested that electromagnetic stimulations can enhance oligodendrocyte differentiation and myelination of axons (Prasad et al. 2017; Lee et al. 2017). It is possible that FES may also facilitate cellular changes like myelination in SCI patients. Molecularly, FES can facilitate muscle fiber conversion to fatigue resistant and aerobic types while activating metabolic genes and reducing the risk factors for diabetes. Continued research would streamline the use of FES in SCI rehabilitation and provide more evidence to further elucidate the underlying mechanisms.

In summary, FES has shown to be beneficial for SCI patients by improving respiration, circulation, hand strength, mobility, and metabolism; and its mechanism can be explained by the theories of Hebbian neuronal network activation and adaptive plasticity, as well as the role of central pattern generators.

Acknowledgements We would like to thank Johns Hopkins Welch Medical Library Informationist Mr. Robert Wright, MLS for providing his expertise and assistance with the PubMed database search. We would also like to acknowledge the contributions of Ms. Alisa Brown, Mr. Michael Pozin, Ms. Nausheen Tickoo, and Ms. Shichen Zhang for their efforts of preliminary literature search and data mining. The illustrations of this article were created with Biorender.com following an academic licensing agreement.

Author Contributions AA, SL, HX and YZ contributed to the conception and design. SL, HX and YZ performed literature search and data analysis. SL and HX drafted the paper. XL provided critical revision of the work. AA supervised and reviewed this study.

Funding The study received no external funding.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

References

Agrawal, G., Sherman, D., Maybhate, A., Gorelik, M., Kerr, D. A., Thakor, N. V., et al. (2010). Slope analysis of somatosensory evoked potentials in spinal cord injury for detecting contusion injury and focal demyelination. *Journal of Clinical Neuroscience, 17*(9), 1159–1164. https://doi.org/10.1016/j.jocn.2010.02.005.

Agrawal, G., Sherman, D., Thakor, N., & All, A. (2008). A novel shape analysis technique for somatosensory evoked potentials. In *2008 30th Annual International Conference of the IEEE Engineering in Medicine and Biology Society, 1–8*, (p. 4688). https://doi.org/10.1109/Iembs.2008.4650259

Al-Nashash, H., Fatoo, N. A., Mirza, N. N., Ahmed, R. I., Agrawal, G., Thakor, N. V., et al. (2009). Spinal cord injury detection and monitoring using spectral coherence. *IEEE Transactions on Biomedical Engineering, 56*(8), 1971–1979. https://doi.org/10.1109/Tbme.2009.2018296.

All, A. H., Bazley, F. A., Gupta, S., Pashai, N., Hu, C., Pourmorteza, A., et al. (2012). Human embryonic stem cell-derived oligodendrocyte progenitors aid in functional recovery of sensory pathways following contusive spinal cord injury. *PLoS ONE, 7*(10), e47645. https://doi.org/10.1371/journal.pone.0047645.

Ambrosini, E., Ferrante, S., Schauer, T., Ferrigno, G., Molteni, F., & Pedrocchi, A. (2010). Design of a symmetry controller for cycling induced by electrical stimulation: Preliminary results on post-acute stroke patients. *Artificial Organs*. https://doi.org/10.1111/j.1525-1594.2009.00941.x.

American Spinal Injury Association. (2002). International standards for neurological classification of SCI. *The Journal of Spinal Cord Medicine, 34*, 535–546.

Baker, L. L., Bowman, B. R., & McNeal, D. R. (1988). Effects of waveform on comfort during neuromuscular electrical stimulation. *Clinical Orthopaedics and Related Research, 233*, 75–85.

Bakkum, A. J., de Groot, S., Stolwijk-Swuste, J. M., van Kuppevelt, D. J., van der Woude, L. H., et al. (2015). Effects of hybrid cycling versus handcycling on wheelchair-specific fitness and physical activity in people with long-term spinal cord injury: A 16-week randomized controlled trial. *Spinal Cord, 53*(5), 395–401. https://doi.org/10.1038/sc.2014.237.

Bareyre, F. M., Kerschensteiner, M., Raineteau, O., Mettenleiter, T. C., Weinmann, O., & Schwab, M. E. (2004). The injured spinal cord spontaneously forms a new intraspinal circuit in adult rats. *Nature Neuroscience, 7*(3), 269–277. https://doi.org/10.1038/nn1195.

Bazley, F. A., All, A. H., Thakor, N. V., & Maybhate, A. (2011). Plasticity associated changes in cortical somatosensory evoked potentials following spinal cord injury in rats. In *Annual International Conference of the IEEE Engineering in Medicine and Biology Society (Embc),* (pp. 2005–2008).

Bellman, M. J., Cheng, T. H., Downey, R. J., & Dixon, W. E. (2014). Stationary cycling induced by switched functional electrical stimulation control. In *American Control Conference (Acc),* (pp. 4802–4809).

Bergquist, A. J., Clair, J. M., Lagerquist, O., Mang, C. S., Okuma, Y., & Collins, D. F. (2011). Neuromuscular electrical stimulation: Implications of the electrically evoked sensory volley. *European Journal of Applied Physiology, 111*(10), 2409–2426. https://doi.org/10.1007/s00421-011-2087-9.

Bersch, I., & Friden, J. (2016). Role of functional electrical stimulation in tetraplegia hand surgery. *Archives of Physical Medicine and Rehabilitation, 97*(6 Suppl), S154–159. https://doi.org/10.1016/j.apmr.2016.01.035.

Bhadra, N., & Peckham, P. H. (1997). Peripheral nerve stimulation for restoration of motor function. *Journal of Clinical Neurophysiology, 14*(5), 378–393.

Bickel, C. S., Slade, J. M., VanHiel, L. R., Warren, G. L., & Dudley, G. A. (2004). Variable-frequency-train stimulation of skeletal muscle after spinal cord injury. *Journal of Rehabilitation Research and Development, 41*(1), 33–40.

Brindley, G. S. (1977). An implant to empty the bladder or close the urethra. *Journal of Neurology, Neurosurgery and Psychiatry, 40*(4), 358–369. https://doi.org/10.1136/jnnp.40.4.358.

Carel, C., Loubinoux, I., Boulanouar, K., Manelfe, C., Rascol, O., Celsis, P., et al. (2000). Neural substrate for the effects of passive training on sensorimotor cortical representation: A study with functional magnetic resonance imaging in healthy subjects. *Journal of Cerebral Blood Flow & Metabolism, 20*(3), 478–484.

Coupaud, S., Gollee, H., Hunt, K. J., Fraser, M. H., Allan, D. B., & McLean, A. N. (2008). Arm-cranking exercise assisted by Functional Electrical Stimulation in C6 tetraplegia: A pilot study. *Technology and Health Care, 16*(6), 415–427.

Creasey, G. H., & Craggs, M. D. (2012). Functional electrical stimulation for bladder, bowel, and sexual function. *Handbook of Clinical Neurology, 109*, 247–257. https://doi.org/10.1016/B978-0-444-52137-8.00015-2.

Dancause, N., & Nudo, R. J. (2011). Shaping plasticity to enhance recovery after injury. *Progress in Brain Research, 192*, 273–295. https://doi.org/10.1016/B978-0-444-53355-5.00015-4.

de Kroon, J. R., IJzerman, M. J., Chae, J., Lankhorst, G. J., & Zilvold, G. (2005). Relation between stimulation characteristics and clinical outcome in studies using electrical stimulation to improve motor control of the upper extremity in stroke. *Journal of Rehabilitation Medicine, 37*, 65–74.

Deley, G., Denuziller, J., Babault, N., & Taylor, J. A. (2015). Effects of electrical stimulation pattern on quadriceps isometric force and fatigue in individuals with spinal cord injury. *Muscle and Nerve, 52*(2), 260–264. https://doi.org/10.1002/mus.24530.

Dimitrijevic, M. R., Gerasimenko, Y., & Pinter, M. M. (1998). Evidence for a spinal central pattern generator in humans. *Annals of the New York Academy of Sciences, 860*, 360–376. https://doi.org/10.1111/j.1749-6632.1998.tb09062.x.

Dobkin, B. H. (2003). Do electrically stimulated sensory inputs and movements lead to long-term plasticity and rehabilitation gains? *Current Opinion in Neurology, 16*(6), 685–691.

Doucet, B. M., Lam, A., & Griffin, L. (2012). Neuromuscular electrical stimulation for skeletal muscle function. *The Yale Journal of Biology and Medicine, 85*(2), 201–215.

Downey, R. J., Bellman, M., Sharma, N., Wang, Q., Gregory, C. M., & Dixon, W. E. (2011). A novel modulation strategy to increase stimulation duration in neuromuscular electrical stimulation. *Muscle and Nerve, 44*(3), 382–387. https://doi.org/10.1002/mus.22058.

Downey, R. J., Bellman, M. J., Kawai, H., Gregory, C. M., & Dixon, W. E. (2014). Comparing the induced muscle fatigue between asynchronous and synchronous electrical stimulation in able-bodied and spinal cord injured populations. *IEEE Transactions on Neural Systems and Rehabilitation Engineering, 23*(6), 964–972.

Eser, P. C., Donaldson Nde, N., Knecht, H., & Stussi, E. (2003). Influence of different stimulation frequencies on power output and fatigue during FES-cycling in recently injured SCI people. *IEEE Transactions on Neural Systems and Rehabilitation Engineering, 11*(3), 236–240. https://doi.org/10.1109/TNSRE.2003.817677.

Ethier, C., Gallego, J., & Miller, L. E. (2015). Brain-controlled neuromuscular stimulation to drive neural plasticity and functional recovery. *Current Opinion in Neurobiology, 33*, 95–102.

Fazio, C. (2014). Functional electrical stimulation for incomplete spinal cord injury. *Baylor University Medical Center Proceedings, 27*(4), 353–355. https://doi.org/10.1080/08998280.2014.11929157.

Ferrante, S., Ambrosini, E., Ferrigno, G., & Pedrocchi, A. (2012). Biomimetic NMES controller for arm movements supported by a passive exoskeleton. In *Annual International Conference of the IEEE Engineering in Medicine and Biology Society (Embc),* (pp. 1888–1891).

Figoni, S. F. (1990). Perspectives on cardiovascular fitness and SCI. *The Journal of the American Paraplegia Society, 13*(4), 63–71.

Furlan, J. C., & Fehlings, M. G. (2008). Cardiovascular complications after acute spinal cord injury: Pathophysiology, diagnosis, and management. *Neurosurgical Focus*. https://doi.org/10.3171/Foc.2008.25.11.E13.

Gargiulo, P., Reynisson, P. J., Helgason, B., Kern, H., Mayr, W., Ingvarsson, P., et al. (2011). Muscle, tendons, and bone: Structural changes during denervation and FES treatment. *Neurological Research, 33*(7), 750–758. https://doi.org/10.1179/1743132811Y.0000000007.

Gater, D. R., Jr., Dolbow, D., Tsui, B., & Gorgey, A. S. (2011). Functional electrical stimulation therapies after spinal cord injury. *NeuroRehabilitation, 28*(3), 231–248. https://doi.org/10.3233/NRE-2011-0652.

Gilman, S., & Arbor, A. (1983). Handbook of physiology. Section 1: The nervous system, vol II. Motor control, parts 1 and 2. Section editors: John M. Brookhart and Vernon B. Mountcastle volume editor: Vernon B. Brooks Bethesda, MD, American Physiological Society, 1981 1480 pp, illustrated. *Annals of Neurology, 13*(1), 111–111. https://doi.org/10.1002/ana.410130130.

Gorgey, A. S., Black, C. D., Elder, C. P., & Dudley, G. A. (2009). Effects of electrical stimulation parameters on fatigue in skeletal muscle. *Journal of Orthopaedic and Sports Physical Therapy, 39*(9), 684–692. https://doi.org/10.2519/jospt.2009.3045.

Gorgey, A. S., & Dudley, G. A. (2008). The role of pulse duration and stimulation duration in maximizing the normalized torque during neuromuscular electrical stimulation. *Journal of Orthopaedic and Sports Physical Therapy, 38*(8), 508–516. https://doi.org/10.2519/jospt.2008.2734.

Gorgey, A. S., Graham, Z. A., Bauman, W. A., Cardozo, C., & Gater, D. R. (2017). Abundance in proteins expressed after functional electrical stimulation cycling or arm cycling ergometry training in persons with chronic spinal cord injury. *Journal of Spinal Cord Medicine, 40*(4), 439–448. https://doi.org/10.1080/10790268.2016.1229397.

Gorgey, A. S., & Lawrence, J. (2016). Acute responses of functional electrical stimulation cycling on the ventilation-to-CO_2 production ratio and substrate utilization after spinal cord injury. *PM R, 8*(3), 225–234. https://doi.org/10.1016/j.pmrj.2015.10.006.

Griffin, L., Decker, M. J., Hwang, J. Y., Wang, B., Kitchen, K., Ding, Z., et al. (2009). Functional electrical stimulation cycling improves body composition, metabolic and neural factors in persons with spinal cord injury. *Journal of Electromyography and Kinesiology, 19*(4), 614–622. https://doi.org/10.1016/j.jelekin.2008.03.002.

Griffiths, I. R., & Miller, R. (1974). Vascular permeability to protein and vasogenic oedema in experimental concussive injuries to the canine spinal cord. *Journal of the Neurological Sciences, 22*(3), 291–304.

Grill, W. M., Jr., & Mortimer, J. T. (1996). The effect of stimulus pulse duration on selectivity of neural stimulation. *IEEE Transactions on Biomedical Engineering, 43*(2), 161–166. https://doi.org/10.1109/10.481985.

Grillner, S., & Wallen, P. (1985). Central pattern generators for locomotion, with special reference to vertebrates. *Annual Review of Neuroscience, 8*, 233–261. https://doi.org/10.1146/annurev.ne.08.030185.001313.

Guertin, P. A. (2012). Central pattern generator for locomotion: Anatomical, physiological, and pathophysiological considerations. *Frontiers in Neurology, 3*, 183. https://doi.org/10.3389/fneur.2012.00183.

Hamid, S., & Hayek, R. (2008). Role of electrical stimulation for rehabilitation and regeneration after spinal cord injury: An overview. *European Spine Journal, 17*(9), 1256–1269. https://doi.org/10.1007/s00586-008-0729-3.

Hansen, C. N., Faw, T. D., White, S., Buford, J. A., Grau, J. W., & Basso, D. M. (2016). Sparing of descending axons rescues interneuron plasticity in the lumbar cord to allow adaptive learning after thoracic spinal cord injury. *Frontiers in Neural Circuits*. https://doi.org/10.3389/fncir.2016.00011.

Hebb, D. (1949). *The organization of behavior*. New York: Wiley.

Ho, C. H., Triolo, R. J., Elias, A. L., Kilgore, K. L., DiMarco, A. F., Bogie, K., et al. (2014). Functional Electrical Stimulation and Spinal Cord Injury. *Physical Medicine and Rehabilitation Clinics of North America,25* (3), 631–654. https://doi.org/10.1016/j.pmr.2014.05.001.

Ibitoye, M. O., Hamzaid, N. A., Hasnan, N., Abdul Wahab, A. K., & Davis, G. M. (2016). Strategies for rapid muscle fatigue reduction during FES exercise in individuals with spinal cord injury: A systematic review. *PLoS ONE, 11*(2), e0149024. https://doi.org/10.1371/journal.pone.0149024

Itoh, S., Ohta, T., Sekino, Y., Yukawa, Y., & Shinomiya, K. (2008). Treatment of distal radius fractures with a wrist-bridging external fixation: The value of alternating electric current stimulation. *Journal of Hand Surgery, 33*(5), 605–608. https://doi.org/10.1177/1753193408092253.

Kapadia, N., Masani, K., Catharine Craven, B., Giangregorio, L. M., Hitzig, S. L., Richards, K., et al. (2014a). A randomized trial of functional electrical stimulation for walking in incomplete spinal cord injury: Effects on walking competency. *Journal of Spinal Cord Medicine, 37*(5), 511–524. https://doi.org/10.1179/2045772314Y.0000000263.

Kapadia, N. M., Bagher, S., & Popovic, M. R. (2014b). Influence of different rehabilitation therapy models on patient outcomes: Hand function therapy in individuals with incomplete SCI. *Journal of Spinal Cord Medicine, 37*(6), 734–743. https://doi.org/10.1179/2045772314Y.0000000203.

Kebaetse, M. B., Turner, A. E., & Binder-Macleod, S. A. (2002). Effects of stimulation frequencies and patterns on performance of repetitive, nonisometric tasks. *Journal of Applied Physiology, 92*(1), 109–116. https://doi.org/10.1152/jappl.2002.92.1.109.

Kilgore, K. L., Hoyen, H. A., Bryden, A. M., Hart, R. L., Keith, M. W., & Peckham, P. H. (2008). An implanted upper-extremity neuroprosthesis using myoelectric control. *Journal of Hand Surgery-American Volume, 33a*(4), 539–550. https://doi.org/10.1016/j.jhsa.2008.01.007.

Kjaer, M., Perko, G., Secher, N. H., Boushel, R., Beyer, N., Pollack, S., et al. (1994). Cardiovascular and ventilatory responses to electrically induced cycling with complete epidural anaesthesia in humans. *Acta Physiologica Scandinavica, 151*(2), 199–207. https://doi.org/10.1111/j.1748-1716.1994.tb09738.x.

Kobetic, R., To, C. S., Schnellenberger, J. R., Audu, M. L., Bulea, T. C., Gaudio, R., et al. (2009). Development of hybrid orthosis for standing, walking, and stair climbing after spinal cord injury. *Journal of Rehabilitation Research and Development, 46*(3), 447–462.

Koyuncu, E., Nakipoglu-Yuzer, G. F., Dogan, A., & Ozgirgin, N. (2010). The effectiveness of functional electrical stimulation for the treatment of shoulder subluxation and shoulder pain in hemiplegic patients: A randomized controlled trial. *Disability and Rehabilitation, 32*(7), 560–566. https://doi.org/10.3109/09638280903183811.

Kralj, A. R., & Bajd, T. (1989). *Functional electrical stimulation: Standing and walking after spinal cord injury*. Boca Raton: CRC Press.

Lee, H. U., Blasiak, A., Agrawal, D. R., Loong, D. T. B., Thakor, N. V., All, A. H., et al. (2017). Subcellular electrical stimulation of neurons enhances the myelination of axons by oligodendrocytes. *PLoS ONE, 12*(7), e0179642. https://doi.org/10.1371/journal.pone.0179642.

Loong, D. B., Chua, S. M., Prasad, A., Kakkos, I., Jiang, W. X., Yue, M., et al. (2018). Neuroprotective assessment of prolonged local hypothermia post contusive spinal cord injury in rodent model. *Spine Journal, 18*(3), 507–514. https://doi.org/10.1016/j.spinee.2017.10.066.

Lynch, C. L., & Popovic, M. R. (2008). Functional electrical stimulation. *IEEE Control Systems Magazine, 28*(2), 40–50.

Maffiuletti, N. A., Pensini, M., & Martin, A. (2002). Activation of human plantar flexor muscles increases after electromyostimulation training. *Journal of Applied Physiology, 92*(4), 1383–1392. https://doi.org/10.1152/japplphysiol.00884.2001.

Mangold, S., Keller, T., Curt, A., & Dietz, V. (2005). Transcutaneous functional electrical stimulation for grasping in subjects with cervical spinal cord injury. *Spinal Cord, 43*(1), 1–13. https://doi.org/10.1038/sj.sc.3101644.

Marder, E., & Bucher, D. (2001). Central pattern generators and the control of rhythmic movements. *Current Biology, 11*(23), R986–996.

Martin, R., Sadowsky, C., Obst, K., Meyer, B., & McDonald, J. (2012). Functional electrical stimulation in spinal cord injury: From theory to practice. *Topics in Spinal Cord Injury Rehabilitation, 18*(1), 28–33.

Maybhate, A., Hu, C., Bazley, F. A., Yu, Q. L., Thakor, N. V., Kerr, C. L., et al. (2012). Potential long-term benefits of acute hypothermia after spinal cord injury: Assessments with somatosensory-evoked potentials. *Critical Care Medicine, 40*(2), 573–579. https://doi.org/10.1097/CCM.0b013e318232d97e.

McCoin, J. L., Bhadra, N., & Gustafson, K. J. (2013). Electrical stimulation of sacral dermatomes can suppress aberrant urethral reflexes in felines with chronic spinal cord injury. *Neurourology and Urodynamics, 32*(1), 92–97.

Med, C. S. C. (2008). Early acute management in adults with spinal cord injury: A clinical practice guideline for health-care professionals. *Journal of Spinal Cord Medicine, 31*(4), 403–479.

Menendez, H., Ferrero, C., Martin-Hernandez, J., Figueroa, A., Marin, P. J., & Herrero, A. J. (2016). Acute effects of simultaneous electromyostimulation and vibration on leg blood flow in spinal cord injury. *Spinal Cord, 54*(5), 383–389. https://doi.org/10.1038/sc.2015.181.

Mesin, L., Merlo, E., Merletti, R., & Orizio, C. (2010). Investigation of motor unit recruitment during stimulated contractions of tibialis anterior muscle. *Journal of Electromyography and Kinesiology, 20*(4), 580–589. https://doi.org/10.1016/j.jelekin.2009.11.008.

Mir, H., Al-Nashash, H., Kerr, D., Thakor, N., & All, A. (2010). Histogram based quantification of spinal cord injury level using somatosensory evoked potentials. In *Annual International Conference of the IEEE Engineering in Medicine and Biology Society (Embc),*, (pp. 4942–4945). https://doi.org/10.1109/Iembs.2010.5627238.

Mir, H., Al-Nashash, H., Kortelainen, J., & All, A. (2018). Novel Modeling of somatosensory evoked potentials for the assessment of spinal cord injury. *IEEE Transactions on Biomedical Engineering, 65*(3), 511–520. https://doi.org/10.1109/Tbme.2017.2700498.

Moe, J. H., & Post, H. W. (1962). Functional electrical stimulation for ambulation in hemiplegia. *Journal-Lancet, 82*(7), 285–290.

Mohr, T., Andersen, J. L., Biering-Sorensen, F., Galbo, H., Bangsbo, J., Wagner, A., et al. (1997). Long-term adaptation to electrically induced cycle training in severe spinal cord injured individuals. *Spinal Cord, 35*(1), 1–16.

Moritz, C. T., Perlmutter, S. I., & Fetz, E. E. (2008). Direct control of paralysed muscles by cortical neurons. *Nature, 456*(7222), 639–642. https://doi.org/10.1038/nature07418.

Moxon, K. A., Oliviero, A., Aguilar, J., & Foffani, G. (2014). Cortical reorganization after spinal cord injury: Always for good? *Neuroscience, 283*, 78–94.

National Cancer Institute. (n.d.). *NCI dictionary of cancer terms*. https://www.cancer.gov/publications/dictionaries/cancer-terms/def/nmes.

Center, N. S. C. I. S. (2019). *Facts and figures at a glance*. Birmingham, AL: University of Alabama at Birmingham.

NINDS. (2013). *Spinal cord injury: Hope through research*. Bethesda: NIH Publication.

Norenberg, M. D., Smith, J., & Marcillo, A. (2004). *The pathology of human spinal cord injury: Defining the problems*. New Rochelle: Mary Ann Liebert, Inc.

Nuwer, M. R. (1998). Fundamentals of evoked potentials and common clinical applications today. *Electroencephalography and Clinical Neurophysiology, 106*(2), 142–148. https://doi.org/10.1016/S0013-4694(97)00117-X.

Ojha, R., George, J., Chandy, B. R., Tharion, G., & Devasahayam, S. R. (2015). Neuromodulation by surface electrical stimulation of peripheral nerves for reduction of detrusor overactivity in patients with spinal cord injury: A pilot study. *Journal of Spinal Cord Medicine, 38*(2), 207–213. https://doi.org/10.1179/2045772313Y.0000000175.

Okada, S. (2016). The pathophysiological role of acute inflammation after spinal cord injury. *Inflammation and Regeneration*. https://doi.org/10.1186/s41232-016-0026-1.

Partida, E., Mironets, E., Hou, S., & Tom, V. J. (2016). Cardiovascular dysfunction following spinal cord injury. *Neural Regeneration Research, 11*(2), 189.

Peckham, P. H., & Knutson, J. S. (2005). Functional electrical stimulation for neuromuscular applications. *Annual Review of Biomedical Engineering, 7*, 327–360. https://doi.org/10.1146/annurev.bioeng.6.040803.140103.

Petrie, M., Suneja, M., & Shields, R. K. (2015). Low-frequency stimulation regulates metabolic gene expression in paralyzed muscle. *Journal of Applied Physiology, 118*(6), 723–731. https://doi.org/10.1152/japplphysiol.00628.2014.

Prasad, A., Teh, D. B. L., Blasiak, A., Chai, C., Wu, Y., Gharibani, P. M., et al. (2017). Static magnetic field stimulation enhances oligodendrocyte differentiation and secretion of neurotrophic factors. *Scientific Reports, 7*(1), 6743. https://doi.org/10.1038/s41598-017-06331-8.

Price, C. I., & Pandyan, A. D. (2000). Electrical stimulation for preventing and treating post-stroke shoulder pain. *Cochrane Database Systematic Reviews*. https://doi.org/10.1002/14651858.CD001698.

Ragnarsson, K. T. (2008). Functional electrical stimulation after spinal cord injury: Current use, therapeutic effects and future directions. *Spinal Cord, 46*(4), 255–274. https://doi.org/10.1038/sj.sc.3102091.

Ralston, K. E., Harvey, L. A., Batty, J., Lee, B. B., Ben, M., Cusmiani, R., et al. (2013). Functional electrical stimulation cycling has no clear effect on urine output, lower limb swelling, and spasticity in people with spinal cord injury: A randomised cross-over trial. *Journal of Physiotherapy, 59*(4), 237–243.

Righetti, L., Buchli, J., & Ijspeert, A. J. (2006). Dynamic hebbian learning in adaptive frequency oscillators. *Physica D: Nonlinear Phenomena, 216*(2), 269–281.

Roberts, T. T., Leonard, G. R., & Cepela, D. J. (2017). Classifications in brief: American Spinal Injury Association (ASIA) Impairment Scale. *Clinical Orthopaedics and Related Research, 475*(5), 1499–1504. https://doi.org/10.1007/s11999-016-5133-4.

Robinson, A. J. (2008). *Clinical electrophysiology: Electrotherapy and electrophysiologic testing*. Philadelphia: Lippincott Williams & Wilkins.

Rossignol, S. (2000). Locomotion and its recovery after spinal injury. *Current Opinion in Neurobiology, 10*(6), 708–716.

Sabut, S. K., Sikdar, C., Kumar, R., & Mahadevappa, M. (2011). Functional electrical stimulation of dorsiflexor muscle: Effects on dorsiflexor strength, plantarflexor spasticity, and motor recovery in stroke patients. *NeuroRehabilitation, 29*(4), 393–400. https://doi.org/10.3233/NRE-2011-0717.

Sahin, N., Ugurlu, H., & Albayrak, I. (2012). The efficacy of electrical stimulation in reducing the post-stroke spasticity: A randomized controlled study. *Disability and Rehabilitation, 34*(2), 151–156. https://doi.org/10.3109/09638288.2011.593679.

Salameh, A., Al Mohajer, M., & Daroucihe, R. O. (2015). Prevention of urinary tract infections in patients with spinal cord injury. *CMAJ, 187*(11), 807–811.

Sieck, G. C., & Mantilla, C. B. (2004). Influence of sex hormones on the neuromuscular junction. In *Advances in molecular and cell biology* (Vol. 34, pp. 183–194). Amsterdam: Elsevier.

Sluka, K. A., & Walsh, D. (2003). Transcutaneous electrical nerve stimulation: Basic science mechanisms and clinical effectiveness. *Journal of Pain, 4*(3), 109–121.

Stein, R. B., Everaert, D. G., Thompson, A. K., Chong, S. L., Whittaker, M., Robertson, J., et al. (2010). Long-term therapeutic and orthotic effects of a foot drop stimulator on walking performance in progressive and nonprogressive neurological disorders. *Neurorehabilitation and Neural Repair, 24*(2), 152–167. https://doi.org/10.1177/1545968309347681.

Szecsi, J., Fornusek, C., Krause, P., & Straube, A. (2007). Low-frequency rectangular pulse is superior to middle frequency alternating current stimulation in cycling of people with spinal cord injury. *Archives of Physical Medicine and Rehabilitation, 88*(3), 338–345.

Tator, C. H., & Koyanagi, I. (1997). Vascular mechanisms in the pathophysiology of human spinal cord injury. *Journal of Neurosurgery, 86*(3), 483–492. https://doi.org/10.3171/jns.1997.86.3.0483.

Thijssen, D. H., Ellenkamp, R., Smits, P., & Hopman, M. T. (2006). Rapid vascular adaptations to training and detraining in persons with spinal cord injury. *Archives of Physical Medicine and Rehabilitation, 87*(4), 474–481. https://doi.org/10.1016/j.apmr.2005.11.005.

Thorsen, R., Dalla Costa, D., Chiaramonte, S., Binda, L., Beghi, E., Redaelli, T., et al. (2013). A noninvasive neuroprosthesis augments hand grasp force in individuals with cervical spinal cord injury: The functional and therapeutic effects. *Scientific World Journal, 2013*, 836959. https://doi.org/10.1155/2013/836959.

Thrasher, A., Graham, G. M., & Popovic, M. R. (2005). Reducing muscle fatigue due to functional electrical stimulation using random modulation of stimulation parameters. *Artificial Organs, 29*(6), 453–458.

Van Duijnhoven, N. T., Janssen, T. W., Green, D. J., Minson, C. T., Hopman, M. T., & Thijssen, D. H. (2009). Effect of functional electrostimulation on impaired skin vasodilator responses to local heating in spinal cord injury. *Journal of Applied Physiology,* *106*(4), 1065–1071. https://doi.org/10.1152/japplphysiol.91611.2008.

Vipin, A., Thow, X. Y., Mir, H., Kortelainen, J., Manivannan, J., Al-Nashash, H., et al. (2016). Natural progression of spinal cord transection injury and reorganization of neural pathways. *Journal of Neurotrauma, 33*(24), 2191–2201. https://doi.org/10.1089/neu.2015.4383.

Wahls, T. L., Reese, D., Kaplan, D., & Darling, W. G. (2010). Rehabilitation with neuromuscular electrical stimulation leads to functional gains in ambulation in patients with secondary progressive and primary progressive multiple sclerosis: A case series report. *Journal of Alternative and Complementary Medicine, 16*(12), 1343–1349. https://doi.org/10.1089/acm.2010.0080.

Wan, J. J., Qin, Z., Wang, P. Y., Sun, Y., & Liu, X. (2017). Muscle fatigue: General understanding and treatment. *Experimental & Molecular Medicine, 49*(10), e384. https://doi.org/10.1038/emm.2017.194.

Wheeler, G. D., Andrews, B., Lederer, R., Davoodi, R., Natho, K., Weiss, C., et al. (2002). Functional electric stimulation-assisted rowing: Increasing cardiovascular fitness through functional electric stimulation rowing training in persons with spinal cord injury. *Archives of Physical Medicine and Rehabilitation, 83*(8), 1093–1099.

Wilbanks, S. R., Rogers, R., Pool, S., & Bickel, C. S. (2016). Effects of functional electrical stimulation assisted rowing on aerobic fitness and shoulder pain in manual wheelchair users with spinal cord injury. *Journal of Spinal Cord Medicine, 39*(6), 645–654. https://doi.org/10.1179/2045772315Y.0000000052.

Yarar-Fisher, C., Bickel, C. S., Windham, S. T., McLain, A. B., & Bamman, M. M. (2013). Skeletal muscle signaling associated with impaired glucose tolerance in spinal cord-injured men and the effects of contractile activity. *Journal of Applied Physiology, 115*(5), 756–764. https://doi.org/10.1152/japplphysiol.00122.2013.

Yasar, E., Yilmaz, B., Goktepe, S., & Kesikburun, S. (2015). The effect of functional electrical stimulation cycling on late functional improvement in patients with chronic incomplete spinal cord injury. *Spinal Cord, 53*(12), 866–869. https://doi.org/10.1038/sc.2015.19.

Young, S., Hampton, S., & Tadej, M. (2011). Study to evaluate the effect of low-intensity pulsed electrical currents on levels of oedema in chronic non-healing wounds. *Journal of Wound Care, 20*(8), 368. https://doi.org/10.12968/jowc.2011.20.8.368.

Young, W. (2015). Electrical stimulation and motor recovery. *Cell Transplantation, 24*(3), 429–446. https://doi.org/10.3727/096368915X686904.