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Neuromodulation for restoring function after spinal cord injury

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Abstract

Neuromodulation -the concept of using electrical interfaces to alter neuronal activity- has been successfully applied as a treatment approach to several neurological disorders, including deep brain stimulation for Parkinson's disease and epidural spinal stimulation for chronic pain. Neuromodulation can also be beneficial for spinal cord injury, from assisting basic functions such as respiratory pacing and bladder control through to restoring volitional movements and skilled hand function. Approaches range from electrical stimulation of peripheral muscles, either directly or via brain-controlled bypass devices, to stimulation of the spinal cord and brain. Limitations to widespread clinical application include durability of neuromodulation devices, affordability and accessibility of some approaches, and limited understanding of the underlying mechanisms. Current efforts to overcome these challenges through advances in technology, together with knowledge gained from recent clinical trials and basic research, may lead to personalised neuromodulatory interventions to meet the specific needs of individuals with spinal cord injury.

Introduction

Pharmacological agents provide the mainstay of treatments for neurological disorders and efforts to improve such treatments continue. However, high attrition rates and costs coupled with a stringent regulatory environment[1–3] has led to a surge in interest in developing alternative approaches, particularly those using various forms of electrical stimulation to augment or modify neuronal function. Collectively known as neuromodulation, these approaches have therapeutic benefit for a variety of neurological disorders[4–6] and recent advances in materials science, battery and microelectronic development, and computing capacity will likely improve their clinical application (e.g. the development of closed-loop adaptive deep brain[7] and vagus nerve[8] stimulation to increase stimulation efficiency). Neuromodulation also presents an attractive option for spinal cord injury (SCI) due to the potential for electrically activating isolated neuronal circuitry below the injury site, which remains intact but can no longer efficiently receive supraspinal input or transmit sensory information for processing by higher centres.[9]

There has been a surge of interest in basic and clinical research investigating spinal stimulation paradigms for restoring function after SCI, with evidence that enhancing spinal excitability using either epidural or transcutaneous stimulation can restore volitional motor output[10]. Advances are also being made in brain stimulation approaches to modulate supraspinal circuitry and drive functional motor output after SCI[11]. While direct electrical stimulation of the peripheral nervous system represents the most established, clinically accessible and well tested form of neuromodulation for SCI (with many functional electrical stimulation devices commercially available and used in the clinic[12,13]), brain machine interfaces are also used to stimulate peripheral nerves or muscle groups using decoded neural signals from the brain[14].

Although growing evidence suggests that neuromodulation-based interventions for SCI can improve a range of functions (e.g. volitional movements of lower limbs[10] and hand dexterity[15]) there are substantial challenges to overcome for widespread clinical application. These relate to accessibility, affordability, durability, feasibility, and scalability of the approaches. A deeper understanding of mechanisms will also be crucial, as will rigorous clinical trial design, including identifying the appropriate clinical group for inclusion and determining the optimal timing of neuromodulation. In this Review, we discuss advances in basic and clinical research and bioengineering that have the potential to overcome some of these challenges and advance the development of neuromodulatory approaches for restoring meaningful function after SCI.

Spinal cord stimulation

A wide range of stimulation devices and neuromodulation approaches, with different modalities and sites of stimulation, are now available for SCI (Figure 1).

Epidural spinal stimulation

Epidural spinal stimulation, involving surgical implantation of electrodes above the dorsal surface of the spinal cord, has been used for decades as an intervention for chronic pain[5,16]. Modest success in alleviating pain has been reported with low frequency stimulation (in the 10-100 hertz range)[16]. However, the presence of paraesthesia[17] (optimal stimulation intensities for the intervention are determined by the intensity at which the subject perceives paraesthesia) has prevented an appropriate sham condition needed for conducting randomised controlled trials. High frequency (in the 1-10 kilohertz range) epidural stimulation delivered at a low intensity has become widespread in pain treatment. Two large clinical trials[17,18] comparing high frequency stimulation with low frequency stimulation have reported improved patient preference and efficacy of pain relief with high frequency stimulation, with success rates of 70-80%. Although high frequency-low intensity epidural spinal stimulation is not consciously perceived, and therefore a sham controlled trial would be possible, these have not typically been conducted. However, a small trial of 24 subjects with axial low back pain comparing varying frequency spinal stimulation in a randomised crossover design reported significant pain relief with 5882 Hz stimulation compared to lower frequencies and sham stimulation[19], and a larger trial for treating neuropathic low back pain is planned (NCT03470766).

Epidural electrodes are quick to implant and have a good safety record[5,17–19]. This has led to several studies exploring other applications of epidural spinal stimulation beyond pain relief, with particular focus on activating spinal circuitry to restore both voluntary and involuntary movement after SCI. Evidence from an initial case study in a participant with a chronic motor-complete American Spinal Injury Association (ASIA) Impairment Scale (AIS) B SCI[20] and in a follow up study of three participants (two with motor and sensory-complete [AIS A] and one AIS B SCI)[10] suggests that epidural stimulation of the lumbosacral spinal cord prior to any training could enable participants to make small voluntary leg movements during the period of stimulation. When stimulation was combined with daily stand, step and voluntary training, participants could generate graded levels of force and sustained contractions upon verbal command during entire leg flexion exercises[10]. Furthermore, progressive improvements were reported in a follow up study of one of the 4 participants (with AIS B SCI) who received continued activity-based interventions over a 44 month period without continuing stimulation[21], suggesting the possibility of ongoing neural adaptations as a result of long-term activity-based training. An independent replication study using a similar design, which demonstrated

improved volitional control of task-specific motor functions with epidural spinal stimulation in a participant with AIS A SCI[22], has fuelled optimism that further development of this approach (e.g. with improved spatiotemporal neuromodulation protocols that reproduce the natural dynamics of motoneuron activation during locomotion[23]) could eventually enable individuals with SCI to produce functionally meaningful motor movements such as improvements in walking function.

The application of epidural stimulation for restoring upper limb function is considered a greater challenge than lower limb, due to movements being less stereotyped and rhythmic and the loss of upper limb motor neurons following cervical SCI[24]. However, a case study of two participants with AIS B cervical SCI reported improvements in grip strength and motor scores one week after daily epidural spinal stimulation[25]. Although this was not a controlled trial, the study illustrates the feasibility of promoting motor recovery of the upper limbs using epidural spinal stimulation. Furthermore, since epidural electrodes now have multiple independent contacts extending over several spinal segments, a rich pattern of stimulation, driving different motor circuits is possible.

Transcutaneous spinal cord stimulation

Transcutaneous spinal cord stimulation (tcSCS), where electrodes are placed on the skin over the vertebral column offering a non-invasive method for potentially activating spinal cord circuitry, has also been explored. Studies have employed brief high frequency current pulses[26] or direct current stimulation[27] and provide evidence that these stimulation approaches can modulate the excitability of spinal and supraspinal circuits[27,28]. Case studies indicate improved upper limb strength and prehension with tcSCS[29] and when delivered at multiple spinal levels in combination with training tcSCS improved volitional stepping-like movements in all 5 participants with chronic motor-complete AIS B SCI[30]. Although there is little available clinical trial data to support tcSCS as an intervention for SCI, the number of registered clinical trials utilising this technique is increasing (Figure 2) and two randomised crossover design trials assessing lower limb function (NCT01949285) and upper limb function (NCT01906424) have been completed (Table 1). TcSCS as a potential therapy is attractive since it is non-invasive, inexpensive and uses conventional, commercially available stimulation devices. Although there is evidence to indicate that both epidural spinal stimulation and tcSCS can target the same neural structures[31], tcSCS is likely to be less accurate in targeting specific areas of the spinal cord compared to sophisticated implanted techniques such as applying epidural spinal stimulation in a targeted spatiotemporal pattern to engage specific muscle synergies at different times in the step cycle[23]. Further understanding of mechanisms of tcSCS will be important for improving its clinical application (Figure 3).

Experimental advances

Ongoing experimental research utilises more invasive and complex spinal stimulation paradigms. For example, a comparison of epidural, subdural and intraspinal stimulation at dorsal and ventral locations on, or in, the cervical spinal cord of rhesus monkeys revealed that differences in selectivity and in the direct or indirect activation of motor neurons could be advantageous in different situations (eg, when facilitating endogenous movements versus directly activating muscle groups), and that this should be taken into account when designing neuroprostheses[32]. A newly developed primate model of paraplegia that can elicit temporary lower extremity paralysis may also be useful for neural interface development and optimisation of stimulating and recording parameters[33]. In rodent SCI models, kinematic feedback and multi-electrode epidural arrays have allowed real-time spatiotemporal neuromodulation of flexor and extensor activity during hindlimb stepping[23], robotic interfaces have been combined with epidural and pharmacological stimulation of the spinal cord to restore hindlimb stepping[34], and activity-based feedback has been used to trigger synchronised intraspinal microstimulation for improving forelimb function[35]. Experimental studies also enable the development and testing of advanced hardware to improve current clinically-available devices, such as the development of flexible electrode arrays for enhanced neural implant longevity[36].

Promising results using spinal cord stimulation have led to an increase in clinical trials for these interventions, with epidural spinal stimulation representing ~9% and tcSCS representing ~15% of all electrical stimulation trials for SCI in the last 5 years, as opposed to 2% and no trials, respectively, prior to 2013 (Figure 2). However, current clinical findings so far have been made in only a small number of case studies and until large-scale clinical trials are carried out, it is not clear how robust these initial findings are, or if there are any potential adverse effects associated with long-term spinal stimulation using parameters optimal for treatment of SCI.

Brain stimulation

Given that even individuals with motor-complete SCI have some residual pathways connecting spinal and supraspinal circuits[9], there is great interest in using brain stimulation to increase descending activity through these pathways and thereby improve volitional control of upper and lower limb functions after SCI.[11]

Transcranial Direct Current Stimulation

Transcranial direct current stimulation (tDCS) is a non-invasive cortical stimulation approach which delivers low direct current via electrodes placed on the head[15,37] and has been widely used in several mental health conditions (eg, major depression, bipolar disorder and obsessive compulsive

disorder[38]). TDCS is typically combined with motor training to promote activity-dependent plasticity (i.e. functional and anatomical plasticity of neurons as a direct result of their electrical activity[39]). A major advantage of tDCS for SCI is that it can be easily integrated into routine clinical upper extremity training, with associated improvements in pinch force, manual dexterity, and skilled force modulation when delivered alongside repetitive task practice[15]. Current density also impacts functional outcomes, with one study suggesting that a tDCS intervention consisting of 2mA current was necessary for an observable effect in a study of 9 participants with tetraplegia[40]. Since SCI typically involves impairment of both upper extremities, anodal stimulation to both motor cortices may be of value for improving hand function. While this approach has been found to be safe, and is associated with improved bimanual coordination in neurologically healthy individuals[41], its value for individuals with SCI has not yet been studied. There is also evidence for added value in combining tDCS with transcranial magnetic stimulation, although again only studied in neurologically healthy individuals[42].

While upper extremity function is more dependent on cortical control than lower extremity function, there is evidence that in individuals with SCI the integrity of the corticospinal tract is a predictor of locomotor function[43]. Studies using tDCS for facilitating walking function are in the early stages with only a single pilot study published to date with inconclusive results[44]. The outcomes of an ongoing clinical trial using tDCS to augment walking-oriented functional training (NCT03237234) will likely inform clinical practice about its usefulness for lower extremity function. While robust evidence supporting the value of tDCS for improving upper and lower limb function is still needed, the non-invasive nature, absence of substantial adverse events (eg, tDCS does not have the risk of seizures associated with transcranial magnetic stimulation)[11], affordability and clinical accessibility of this approach make it an attractive treatment option for SCI. Furthermore, the advent of wearable technologies to deliver tDCS may herald the broader use of these devices[45].

Transcranial Magnetic Stimulation

While studies of repetitive transcranial magnetic stimulation (rTMS) assessing hand function in individuals with tetraplegia are mostly small, the results are promising and further research is warranted[46,47]. The effects of stimulation on cortical activity are state-dependent[39] meaning that the influence of the stimulation depends on the level of cortical excitability at the time that stimulation is delivered. Since motor activity itself results in increased cortical excitability, the outcomes of cortical stimulation studies are likely to be dependent on whether stimulation is integrated with a motor task. In a sham-controlled cross-over study of 11 individuals with SCI and 10 neurologically healthy subjects[46] where rTMS was interleaved with practice of a hand function task, results indicated clinically meaningful effects on performance of a fine motor task and on grasp strength of the target upper

extremity in the subjects with SCI. Clinically meaningful effects were also found in fine motor task performance of the contralateral hand, indicating transfer of the training effects to the non-trained side. Paired associative stimulation combines cortical TMS with peripheral nerve stimulation. In a quasi-experimental (pre-post) study of 19 subjects with tetraplegia, when the cortical impulse is timed to arrive at the spinal motor neuron prior to the peripheral impulse, there is an associated increase in size of the motor evoked potential and improved performance on a hand function test[48]. rTMS may also improve walking function when used as an adjunct to locomotor training, demonstrated in a sham-controlled study of 31 AIS B subjects where increased walking speed and reduced dependence on assistive devices was observed in a larger proportion of the rTMS-treated subjects, although group differences were not significant[49]. These initial results are interesting and may be of clinical value if it is possible to overcome the limitations imposed by the technology and expertise required for this approach.

Experimental advances

Whilst most clinical SCI studies apply non-invasive brain stimulation, the feasibility of invasive approaches can be tested experimentally. For example, motor cortex stimulation with epidurally implanted electrodes can promote recovery of skilled forelimb function following corticospinal tract and spinal contusion injuries in rodents, with recovery attributed to compensatory commissural sprouting from spared corticospinal tract axons[50]. Mechanistic data has also been determined from primate studies, where invasive recordings during cortical TMS revealed a role for the reticulospinal system (which was activated by loud auditory clicks) in hand function[51], leading to the development of non-invasive wearable devices to deliver clicks paired with electrical stimulation of the biceps muscle in healthy subjects[52], with potential future application for individuals with SCI.

While non-invasive activation of cortical targets is advantageous, a lack of consistent effects support further investigation of more localised targeting of cortical and deeper brain structures. Deep brain stimulation (DBS) has been applied experimentally to specifically target sub-cortical locomotor regions in rats, with lasting improvements in hindlimb functions reported in both acute[53] and chronic[54] injuries. It is unknown what anatomical and neuromodulatory effects such stimulation could have if administered over a prolonged period after SCI. However, there is a wealth of data from the field of DBS in treating symptoms of movement disorders such as Parkinson's, dystonia, and essential tremor and as such the surgical techniques and necessary implantable electrodes are already approved, with clinical evidence showing that long term DBS is practical and has an acceptable safety record[55]. Therefore, there is potential to extend DBS to SCI, as both a target for replacement proprioception and sensation[56] and motor control[57]. Indeed, several clinical trials utilising DBS as an intervention for

SCI have been conducted (Figure 2, Table 1) and another trial is recruiting (NCT03053791). Advances in optimising stimulation parameters for DBS which could potentially be applicable to SCI include closed-loop adaptive DBS[7], where a temporal pattern of stimulation is utilised to increase stimulation efficiency over traditional high frequency DBS. However, as with most neuromodulation approaches the mechanisms underlying beneficial effects of DBS are still poorly understood[58], and further studies are warranted.

Brain machine interfaces

The most sophisticated application of neuromodulation for restoring function after SCI are brain-machine (or brain-computer) interfaces (BMIs)[59,60]. The central idea is to record and then decode brain activity, often related to motor intentions, and use this to generate functional outputs. BMIs can be used to drive external prosthetic devices, such as a robotic arm[61], or to directly control motor function, for example by reanimating paralysed muscles with functional electrical stimulation (FES)[62]- a technique which involves the delivery of electrical pulses directly to muscle tissue, or the nerve supplying a muscle, to elicit a contraction and assist in a specific body movement (Figure 1; appendix). Although underlying concepts of BMI have been around since the 1960s, advances in the last 10 years have been remarkable, with cortical control of paralysed muscles and improved grasp demonstrated first in primate experiments[63,64] and now translated to participants with tetraplegia[14,62]. Interfaces utilise implanted electrodes (intracortical, sub-dural or epidural) or non-invasive surface electrodes (EEG or electromyography [EMG]) for extracting neural activity, which is then translated by a computer algorithm. The most advanced control potential has been achieved with intracortical systems, since it was first demonstrated that a chronic tetraplegic participant with intracortical microelectrodes implanted in the M1 arm area could use a BMI system to control a computer cursor[65], to more recent demonstrations of BMI-enabled reach and grasp movements via a robotic arm[61] or direct muscle activation[14,62]. While these types of assistive BMIs aim to bypass the injury, rehabilitative BMIs, whereby goal-oriented tasks are paired with positive feedback (e.g. tactile feedback during training) aim to enhance neuroplasticity and function[59,60]. One small clinical study[66] applied long-term training with a BMI-based gait protocol combined with EEG-controlled exoskeleton devices and reported recovery of somatic sensation and voluntary motor control in all 8 participants with chronic complete paraplegia. This suggests that BMI combined with training has the potential to go beyond the provision of assistive functions and may enable neurological recovery by triggering brain and spinal cord neuroplasticity through mechanisms such as activity dependent- and spike timing dependent-plasticity. However, it should be noted that all participants in the study[66] (but one) could walk with braces at the study start, and all but one still needed braces at the study end, raising the question of

how much the intensive conventional locomotor training contributed to the recovery. Despite these advances in BMI-based approaches, there are still only a relatively small number of case studies and it is currently not feasible for BMI to become widely clinically available for SCI. Barriers to widespread clinical use include the requirement for advanced specialised technology and expertise, and the high costs of BMI research and development[59]. Another concern, and of relevance to all neuromodulation approaches, is longevity and stability of implanted intracortical electrodes, with microelectrode array failure reportedly occurring around 1 year after implantation[59]. Most BMI set-ups also require the subject to be tethered to an external computer. These systems necessitate repositioning of numerous external electrodes prior to every session, need continuous calibration and are not yet suitable for independent use. Advances in wireless devices, currently being utilised in primate studies[67–69], may be a crucial step to more widespread use of this technology. Despite these challenges, the number of BMI-based clinical trials for SCI is increasing (Figure 2), although these are mainly small-scale open-label trials involving low participant numbers (Table 1).

Experimental advances

Although BMI applications have adopted sophisticated recording and stimulating technology, such as implantable intracortical microelectrode arrays together with multiple implanted percutaneous electrodes in the upper extremities (NCT00912041, Table 1)[14], these systems are not yet fully wireless in that they still require an external connection to the computer interface. Progress in the design of multichannel wireless electrocorticography (ECoG) devices offers the potential for completely implantable systems, with initial evidence for wireless control of an arm prosthesis during primate reaching[67]. Subdural or epidurally implanted ECoG electrode arrays offer enhanced spatiotemporal resolution compared to EEG electrodes and are less invasive than intraparenchymal microelectrode arrays[67]. However, this device[67] has only been assessed in one monkey, and it was designed for human skull dimensions so could not be implanted[67]. Another primate study used movable volumetric three-dimensional multielectrode implants, with reported recordings of a broad range of behaviours in freely roaming primates for up to 5 years[68]. Although fully wireless BMIs have so far only been assessed in uninjured primates[67,68], the potential for fully wireless BMI for SCI will become more apparent with clinical trial data. A trial planned for wireless ECoG recording devices to control a motorised exoskeleton in individuals with tetraplegia is eagerly awaited (NCT02550522), although as with all current BMI trials for SCI, this is a small open-label study.

BMI has been combined with direct stimulation of the spinal cord to create a brain-machine-spinal cord interface (BMSCI), with the potential to reanimate upper or lower limbs bilaterally with an implanted electrode array and the added advantage of facilitating activity-dependent plasticity and

neurorehabilitation[70]. Intracortical recordings have been used to modulate stimulation of the spinal cord via an intraspinal microwire array and shown to significantly enhance task-specific upper limb performance in primates[71,72]. For lower limb paralysis, a wireless BMSCI system has been used to translate intracortical recordings into appropriate spatiotemporal patterns of epidural lumbar spinal cord stimulation, with restored weight-bearing stepping in primates reported as early as six days after a unilateral SCI, without the constraints associated with a tethered system[69]. As with other BMIs, one major limitation for these approaches is the extent of hardware necessary for the system to function optimally. Most devices are likely to require extensive streamlining before they could be used outside of the experimental setting.

Since machine learning is rapidly advancing, BMIs and BMSCIs will likely continue to be refined and could ultimately lead to a neuroprosthetic bypass of the injury site capable of registering motor intentions for a wide variety of different movements and producing appropriate neuromodulatory stimulation patterns to match these intentions. However, most available intracortical and intraspinal microwire arrays cause gliosis and physical damage, eventually resulting in loss of recordings and inefficient stimulation[73]. Thus, efforts to improve the biocompatibility of intracortical arrays should be a priority, and various approaches are being explored, including: the utilisation of flexible electrodes which induce less tissue reaction[36]; bioresorbable silicon electrode arrays, which have a lower risk of tissue reactivity and damage compared to conventional ECoG electrodes[74]; and stent-electrode arrays implanted into superficial cortical veins enabling high-fidelity recordings of cortical neural activity comparable to those of more invasive epidural arrays[75]. DBS electrodes could also potentially be used as part of a BMI, although they are more likely to be useful for stimulation purposes, since they will have the same biocompatibility issues as intracortical arrays if utilised for recording, in which sensitivity to the formation of scar tissue is likely to represent a problem[76]. Alternatively, nanotechnology advances suggest nanoelectrode arrays as a viable option for enhancing implant longevity, with enhanced efficiency, smaller size, and reduced inflammatory responses[77].

Mechanisms of action

Realising the full potential of neuromodulation-based interventions will depend crucially on generating an understanding of when and how electrical stimulation may change neuronal function. This improved mechanistic understanding would inform the optimal design of recording and stimulation parameters and likely lead to improved clinical application. The study of spontaneous recovery, which occurs to some degree in almost all individuals with SCI[78], suggests that while regeneration of damaged axons is unlikely, plastic changes in spared ascending and descending connections is feasible[50,79]. Does electrical stimulation promote this type of plasticity? The best

evidence comes from epidural spinal stimulation, which has been widely used as a treatment for chronic pain[5,16]. The low frequency stimulation (ie, range of 10-100 Hz) excites the large myelinated afferents, particularly proprioceptive primary afferents (the largest) in the spinal roots[31,80]. Multiple experimental and theoretical models suggest that activation of other spinal neurons is unlikely with stimuli close to the sensory threshold[80,81]. There is now robust laboratory evidence that activation of proprioceptive (muscle) sensory fibres can promote both short and long-lasting improvements in modulation of spinal motor reflexes[82,83]. Since impaired modulation of reflex excitability impedes the performance of functional activities, improved modulation is associated with greater function. Indeed, this is the assumed mode of action of the process of rehabilitation after injury and is based on the reinforcement of connectivity[84], presumably through the mechanism of synaptic enhancement. Accordingly, the possibility of tailoring the stimulation to activate specific spinal circuits with precise timing based on the needs of the motor task is under investigation[23]. Given the development of multi-electrode stimulation systems, and the relative ease of generating an almost infinite variety of stimulus patterns, this offers a tremendous opportunity to personalise stimulation for individuals with SCI.

There is also evidence, largely derived from diffusion tensor imaging studies[85], suggesting that brain connectivity is enhanced by repeated use of particular circuits. The mechanism of this enhanced connectivity is not entirely established, but evidence points to activity altering the myelination patterns of some CNS pathways, for instance in corpus callosal pathways after learning complex motor tasks[86]. This altered myelination pattern is certainly a plausible mechanism that might contribute to TMS or multiple forms of spinal cord stimulation (eg, epidural and tcSCS), but this is not yet established. tDCS is a separate case because this form of stimulation does not induce action potentials, instead partial depolarisation of cortical neurons is assumed to lead to increased excitability of the affected circuitry, resulting in increased cortical drive through the remaining pathways[87,88]. While substantial progress has been made in understanding mechanisms underpinning some forms of neuromodulation, much remains to be done (Figure 3).

Conclusions and future directions

Neuromodulation for SCI is a rapidly growing field with great potential, evident by an expansion in clinical trials and growing clinical and experimental evidence that neuromodulation-based interventions can elicit significant recovery of multiple functional outcomes, ranging from complex upper limb and hand dexterity to more basic functions such as bladder control[12,14,20,89]. Approaches range from affordable and clinically accessible (e.g. FES, tcSCS), to those requiring extensive technology and expertise (e.g. BMI). The promising results of high-frequency epidural spinal

stimulation for SCI[10,20], compared to the traditionally used low-frequency stimulation, merits the intensive research attention it is currently receiving in both clinical and experimental settings. Scalability is also possible, given the availability of the technology and its application to disorders beyond SCI. Perhaps the most dramatic demonstrations of return of function have been with BMI approaches, which in several small-scale case studies[14,62,64] have enabled reach and grasp movements in individuals with chronic tetraplegia. However, the evidence base for BMI is to date limited and this approach is the most challenging in terms of scalability, due to high costs and specialist technology and expertise required. While this may improve as technology becomes more affordable and portable, this currently precludes large-scale clinical trials using BMI. tcSCS and tDCS both have the potential to be rapidly made available to individuals with SCI on a large scale, offering cost efficient and safe approaches to treating SCI[15,29,30,40]. Although robust evidence for functional improvements with tcSCS and tDCS is not yet available, preliminary data are promising[15,29,30,40]. Thus, while sophisticated technology such as BMIs may be the future, there certainly seems merit in investing in techniques such as tcSCS and tDCS that can provide clinical benefit at low cost and are easily accessible in most hospital settings.

Future directions for neuromodulation-based interventions for SCI will need to overcome several challenges (Panel 1). Refinements are needed for determining the optimal stimulation technique and parameters for differing conditions and priorities. For example, a BMSCI involving intracortical recordings and epidural cervical stimulation may prove to be optimal for enhancing upper limb function but is unlikely to be useful in the restoration of bladder or sexual function, since sensory information relating to these autonomic functions (such as extent of bladder fullness) would need to reach the brain to allow neural recordings for BMI neuromodulation. These autonomic functions are more easily targeted through local circuitry (e.g. sacral nerve stimulation[89]). Improved mechanistic understanding would benefit the future design and optimisation of targeted stimulation approaches. Improvements in biocompatibility of implantable electrodes is also required, particularly in the case of intracortical and intraspinal electrode arrays. Some of these challenges will be overcome with ongoing advances in technology and new avenues being explored, such as printable bioelectronics which have the potential to create personalised and customisable bionic devices by interfacing biological and functional materials[90]. Optogenetic technology may also have an impact, since the capability of selective manipulation of specific neuronal structures following their transduction with light sensing channelrhodopsins offer the potential for specific targeting of multiple deep brain regions[91] and for incorporation into stem cell based integrated neuronal circuits[92]. Advances in materials science, nanotechnology, and biologics, together with ongoing progress in the development of wearable technology and wireless devices, should lead to substantial improvements in stimulation

and recording capacity, specificity, and longevity. Interdisciplinary collaborations will be essential, including biologists, engineers, materials scientists, and neurosurgeons.

Further challenges include designing future neuromodulation intervention trials for SCI, where costs[93], participant selection, and the timing of intervention are important considerations (Panel 2, appendix). Neuromodulation will likely be a powerful adjunct to other therapeutic avenues for restoring function after SCI. Rehabilitative training is the most obvious example, with increasing evidence that neuromodulatory interventions can augment the effects of training[10,15,21,30,66,94]. Additional combinations may also involve a pharmacological component, since additive benefits have been reported with application of monoaminergic agents in combination with tcSCS and robotic step training[30,95]. Future therapy may also involve the use of neuromodulation as an adjunct to emerging regenerative therapies. Clinical trials for pharmacological (NCT02669849)[96], antibody (NCT00406016)[97] and cellular (NCT01739023) therapies, for example, are ongoing and efficacy of these interventions may be substantially improved by neuromodulatory approaches which could aid consolidation of new connections, or act synergistically to enhance neuroplasticity.

While challenges remain, there is nevertheless robust evidence for neuromodulation-mediated recovery following SCI. Given the increasing evidence of efficacy, the wide variety of devices already in development or available for treatment of other disorders, advances in technology and computer capacity, and an increased push for understanding mechanisms, neuromodulation is fast becoming a leading frontrunner for restoring meaningful function after SCI.

Search strategy and selection criteria

Articles for this Review were identified through searches of PubMed from Jan 01 2012 to May 31 2018 and from references from relevant articles and searches of the authors' own files using combinations of the following search terms: "spinal cord injury", "electrical stimulation", "neuromodulaton", "bioelectronic", "electroceutical" "therapeutic stimulation", and "neurorehabilitation". We included only papers written in English. We selected articles on the basis of topical relevance and originality.

Declaration of interests

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Author contributions

NDJ, SBM, ECFF and EJB wrote the article; EJB collated and edited the article, with input from NDJ, SBM, and ECFF; NDJ, SBM and EJB prepared the display items.

Figure Legends

Figure 1: **Neuromodulation approaches for restoring function after spinal cord injury.** Approaches are grouped by the type of tissue stimulated (brain, spinal cord vs peripheral), in addition to the use of brain machine interfaces to bypass the injury. Redrawn with permission from Scott Leighton. *Peripheral stimulation*: reanimation of paralysed muscles via direct muscle or nerve stimulation. *Spinal stimulation:* activation of spinal circuits to restore volitional motor output in upper and lower limbs. *Brain stimulation*: facilitation or suppression of cortical excitability and modulation of supraspinal motor control centres to drive motor output. *Brain machine interface:* bypassing the injury using decoded brain activity to reanimate paralysed muscles or control external devices.

Figure 2: **Clinical trials for electrical stimulation for spinal cord injury** ClinicalTrials.gov was searched for trials pre-2013 (up to Dec, 31st,2012) and post-2013 (Jan 2013 - May 2018) using the search terms "spinal cord injury" combined with one of the following terms: "electrical stimulation", "brain machine interface", "brain computer interface", "epidural spinal stimulation", "transcutaneous spinal stimulation", "brain stimulation", or "peripheral stimulation". Cross-referencing ensured no trial was counted twice; trials listed as withdrawn, suspended, or terminated were not included. Multiple stimulation techniques within a trial were counted separately. Direct comparison of pre- and post-2013 trials highlights a relatively long history of functional electrical stimulation for SCI, with other stimulation techniques such as epidural spinal stimulation, transcutaneous spinal stimulation, and deep brain stimulation occurring within the past 5 years.

Figure 3: Potential mechanisms underlying electrical stimulation applied to brain, spinal cord, and peripheral tissues.

Table 1. Clinical trials assessing neuromodulation interventions for restoring function after SCI. These are a selected sample of registered ongoing or completed clinical trials on ClinicalTrials.gov. Selection was based on highlighting a promising example of each stimulation type discussed in the Review, the extent of information provided in the trial description, and the most recent initiation dates. AIS - American spinal injury association impairment scale (A = complete: no sensory or motor function is preserved in sacral segments; B = sensory incomplete: sensory but not motor function preserved below the neurological level; C = motor incomplete: motor function preserved below the neurological level, with muscle grade below injury <3 for at least half of key muscle functions; D = motor incomplete: motor function preserved below the neurological level, with muscle grade below injury >3 for at least half of key muscle functions). BMI – brain machine interface; CUE - capabilities of upper extremity instrument; DBS – deep brain stimulation; FES – functional electrical stimulation; GRASSP - the graded redefined assessment of strength, sensation and prehension; tDCS - transcranial direct current stimulation; SCI – spinal cord injury; tcSCS – transcutaneous spinal cord stimulation; tDCS - transcranial direct current stimulation; TMS - transcranial magnetic stimulation.

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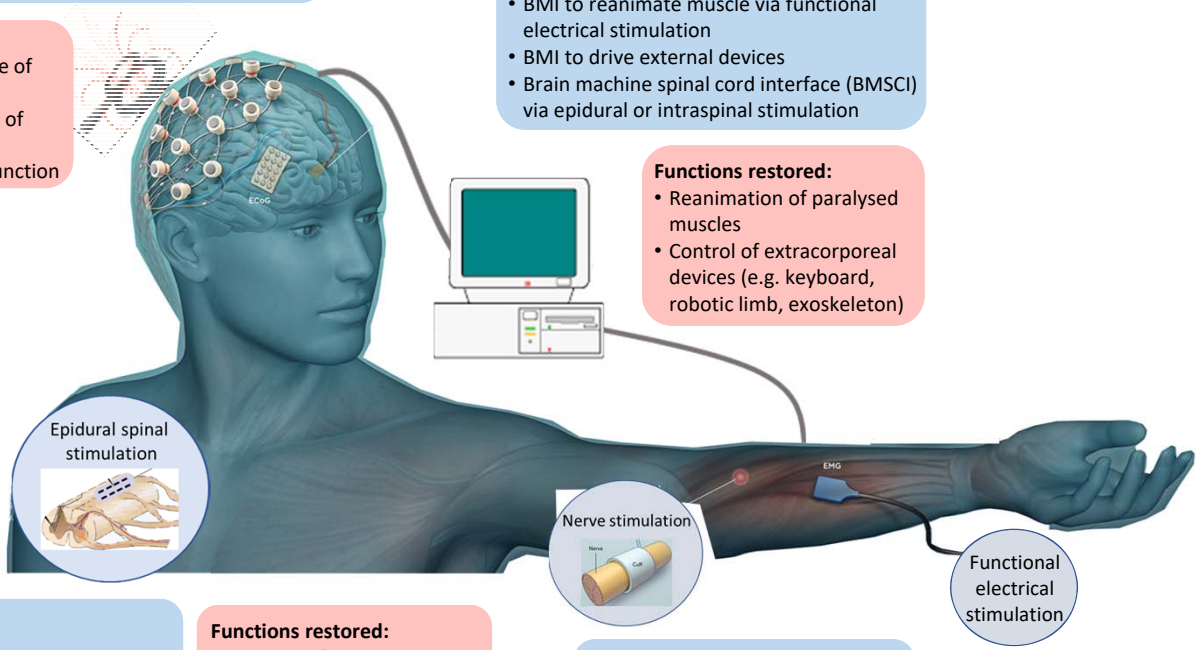
Brain stimulation:
- Transcranial magnetic stimulation
- Transcranial direct current stimulation
- Deep brain stimulation (mainly experimental)
- Epidural stimulation (e.g. motor cortex; experimental)

Functions restored:
- Direct supraspinal drive of motor output
- Excitation or inhibition of supraspinal circuitry
- Predominantly hand function

Brain machine interface (BMI):
- BMI to reanimate muscle via functional electrical stimulation
- BMI to drive external devices
- Brain machine spinal cord interface (BMSCI) via epidural or intraspinal stimulation

Functions restored:
- Reanimation of paralysed muscles
- Control of extracorporeal devices (e.g. keyboard, robotic limb, exoskeleton)

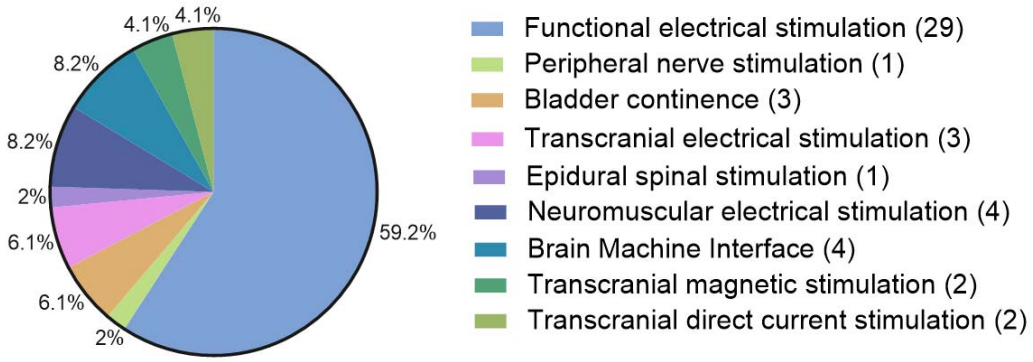


Spinal stimulation:
- Epidural stimulation
- Transcutaneous stimulation
- Intraspinal stimulation (experimental)

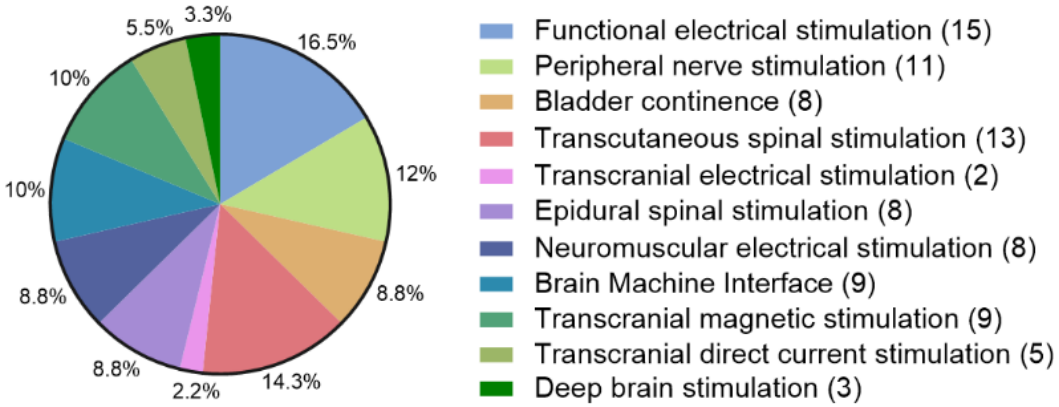
Functions restored:
- Enabling of spinal circuitry to enhance motor output
- Predominantly locomotion

Peripheral stimulation:
- Functional electrical stimulation
- Somatosensory stimulation for motor priming

Functions restored:
- Reanimation of paralysed muscles
- Stepping, reaching and grasping
- Bladder voiding

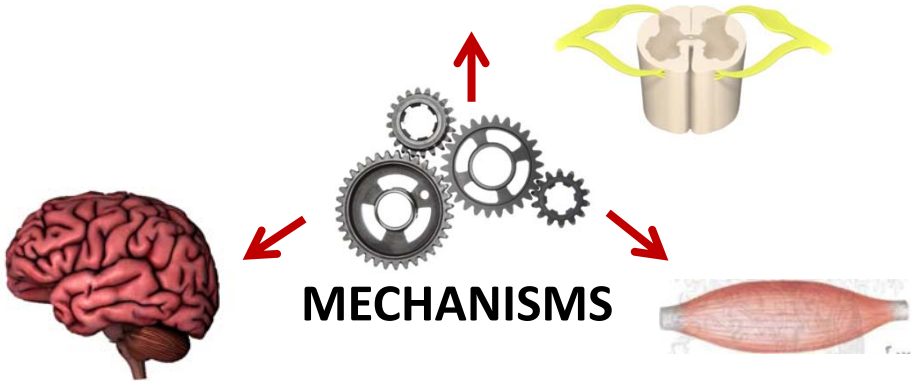


Trials prior to 2013: Total = 49



Trials from Jan 2013 – May 2018: Total = 91

- Modulation of proprioceptive sensory afferents interacts with natural sensory feedback to control motor output[80,81]
- Enhanced activity resulting in increased levels of neuronal growth and neuroplasticity[34]
- Denervation and synaptic silencing leading to “synaptic scaling”[98]



- Changes in connectivity of stimulated pathways due to neuroplasticity, compensatory sprouting and altered myelination patterns[50,79,86]
- Partial depolarisation or hyperpolarisation resulting in increased or decreased excitability[87,88]

- Increased levels of neurotrophic factors leading to plasticity of CNS circuitry[99]
- Increased activation of muscle tissue prevents muscular atrophy and may alter muscle composition[100]

Panel 1: Current challenges of neuromodulation for treating spinal cord injury	
Accessibility	Some approaches are widely available, accessible and transportable (e.g. FES, ESS), whereas others have limited clinical accessibility, require specialised technology and equipment and necessitate the participant being attached to external devices (e.g. TMS, BMI). Advances in wearable technology and wireless devices may improve clinical accessibility
Affordability	Approaches range from relatively cheap devices (e.g. FES, ESS, tcSCS) to those requiring expensive equipment and technology (e.g. robotics, exoskeletons, BMI), which can be prohibitive to widespread use. This may improve with increased availability and the lessening costs of specialised electronics and processors over time
Durability	Maintaining longevity and stability of neuromodulation devices is a major challenge. Advances in technology and the development of new generation electrodes which can maintain long term stability while eliciting minimal gliosis and inflammation will improve durability
Efficacy	Neuromodulation has been reported to improve many functions after SCI, including upper and lower limb functions (FES)[12], bladder voiding (SARS)[89], standing and assisted stepping (ESS)[20] and fine motor control of hand and digit function (BMI)[14]. However, some evidence is less robust, or based on individual case reports and small open-label studies, necessitating the need for larger scale clinical trials
Mechanisms	Better understanding of underlying mechanisms will help to determine optimal stimulation parameters and when and how to manipulate nervous system function with electrical stimulation and should lead to improved efficacy of neuromodulation approaches
Scalability	The above considerations all affect the scalability and potential for widespread clinical use of neuromodulation for treating SCI

BMI – brain machine interface; ESS – epidural spinal stimulation; FES – functional electrical stimulation; SARS – sacral anterior root stimulation; SCI – spinal cord injury; tcSCS – transcutaneous spinal cord stimulation; TMS - transcranial magnetic stimulation.

Panel 2: Future clinical trial design and patient selection for neuromodulation for treatment of spinal cord injury	
Clinical trial design	Considerations for large scale clinical trials for neuromodulation interventions for SCI include costs and healthcare infrastructure required, which can be prohibitive, rigorous trial design, identifying and selecting the appropriate clinical group for inclusion and determining the optimal timing of intervention
Timing of neuromodulation	Trial designs need to consider whether to apply an intervention early after SCI (during a plastic phase) or at a later stage (during a stabilisation phase), particularly when applied in conjunction with a rehabilitation or training component. Differing views are based on different proposed mechanisms[39,101]: *homeostatic plasticity* - would dictate inhibitory stimulation be used in advance of training (where returning excitability to pre-stimulation levels would be synergistic with the activity-related increase in excitability) whereas *principles of gating* - would dictate that excitatory stimulation be used concurrently with training (where the two mechanisms would have an additive effect)
Participant selection	Most stimulation-based clinical trials for SCI enrol individuals with incomplete injuries (some degree of residual spinal transmission to allow sensory perception or volitional movement[43]). Studies[10,20,21] that have enrolled individuals with complete (insufficient residual spinal transmission pathways to allow sensory perception or volitional movement) or discomplete (individuals who appear complete but have some residual remaining transmission when assessed electrophysiologically) injuries have shown that while possible to elicit movement, the technology has yet to facilitate the amount of motor activation required for functional hand or lower extremity activity in these participants