Invited review

Neuroprosthetic technology for individuals with spinal cord injury

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Context: Spinal cord injury (SCI) results in a loss of function and sensation below the level of the lesion. Neuroprosthetic technology has been developed to help restore motor and autonomic functions as well as to provide sensory feedback.

Findings: This paper provides an overview of neuroprosthetic technology that aims to address the priorities for functional restoration as defined by individuals with SCI. We describe neuroprostheses that are in various stages of preclinical development, clinical testing, and commercialization including functional electrical stimulators, epidural and intraspinal microstimulation, bladder neuroprosthesis, and cortical stimulation for restoring sensation. We also discuss neural recording technologies that may provide command or feedback signals for neuroprosthetic devices.

Conclusion/clinical relevance: Neuroprostheses have begun to address the priorities of individuals with SCI, although there remains room for improvement. In addition to continued technological improvements, closing the loop between the technology and the user may help provide intuitive device control with high levels of performance.

Keywords: Spinal cord injuries, Assistive technology, Neural interface, Neuroprosthesis, Brain–computer interface, Electrical stimulation, Epidural stimulation, Central pattern generators, Neurogenic bladder, Paraplegia, Tetraplegia, Rehabilitation

Introduction

Neuroprostheses are devices that use electrodes to interface with the nervous system and aim to restore function that has been lost due to spinal cord injury (SCI). Neuroprostheses can restore some motor, sensory, and autonomic functions by stimulating various parts of the nervous system including muscles, nerves, spinal cord, or the brain. Impairments after high-level SCI can limit a person's ability to use traditional control interfaces like switches, joysticks, or a keyboard and mouse. For that reason, neural interfaces are also being developed to record control signals directly from the nervous system. A few studies have examined priorities for functional restoration as defined by individuals with SCI and found that restoration of arm and hand function is the top priority for individuals with tetraplegia.^{1–3} Restoration of bladder and bowel function, as

well as sexual function, is very important to people with a SCI at any level. Similarly, many people with SCI feel that restoration of walking and/or standing ability would have a positive impact on their quality of life. Here we review different types of neuroprostheses that address these priorities. First we discuss neuroprostheses that stimulate the nervous system in order to restore function or sensation. Next we discuss neural recording interfaces and their potential for providing control or feedback signals for neuroprosthetic technology. Although there are a few devices that are commercially available, we focus on emerging technologies that are in various stages of preclinical and clinical testing.

Stimulation with neuroprostheses

Stimulation of the nervous system has the potential to restore a number of functions that are impaired by SCI. Motor-based functional electrical stimulation (FES) uses electrodes to stimulate muscles or nerves to

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produce muscle contraction and restore motor function. Additionally, direct stimulation of the spinal cord has shown potential for restoring movement. Bladder neuroprostheses stimulate nerves to ameliorate incontinence or voiding dysfunction. Many people with SCI lack normal sensation below the level of the lesion and there has been a recent interest in trying to restore this ability, possibly through direct stimulation of the sensory cortex.

FES to restore movement

A previous study asked people with paraplegia to prioritize the tasks of standing, walking, stair climbing, and transferring.⁴ Walking was listed as the top priority, followed by standing. This study also found that participants were more amenable to implanted technology than visible devices. However, respondents were less likely to indicate that implantation surgery was acceptable. While this seems contradictory, it highlights the importance of aesthetics when designing assistive technology along with the need to document safety and efficacy of devices in order to fully educate the consumers. In a survey related to brain–computer interfaces (BCIs), users indicated that they would prefer to control FES devices for arm and hand function or walking and standing rather than assistive devices like wheelchairs or robotic arm.³ Essentially, people with SCI would prefer to restore function to their own limbs rather than augment function with external hardware. Researchers have prioritized these functions and are working toward safe, implantable devices that are capable of restoring natural movement and ability. For comprehensive reviews of FES applications, see Refs.^{5,6}

FES of muscles after SCI is challenging because of changes that occur in muscle tissue below the level of injury as a result of denervation or disuse. Muscles in this region no longer receive input from the brain and tend to degenerate, losing both strength and volume.⁷ Muscle atrophy can lead to a number of comorbidities including pressure sores and cardiovascular disease. Further, the motor fibers that do remain often undergo a conversion from fatigue-resistant to fast fatigable types.^{8,9} Before FES can provide useful function, it is often necessary to train the muscles to be more fatigue resistant, although there is a tradeoff between muscle endurance and strength. Training often involves stimulation of muscles using surface electrodes a few days per week for a number of months.¹⁰

A variety of electrode types has been explored for FES, including external surface electrodes that are placed on top of the skin, and those that require implantation. Surface electrodes are relatively easy to use and

inexpensive although placement of the electrodes requires skill. Implanted electrodes may target the muscle itself, as with epimysial or intramuscular electrodes, or the nerve innervating the muscle, as with epineural or nerve cuff electrodes. Percutaneous electrodes bridge the gap between surface and implanted electrodes as they are implanted to target the muscle directly, with the lead wires exiting the skin and connecting to an external stimulator. Compared to surface electrodes, implanted electrodes require less electrical charge, allow for great stimulation selectivity, can target deeper muscles, and eliminate the external components that can be difficult to setup and manage and may be aesthetically displeasing. Implanted electrodes connect to an implanted stimulator that communicates outside the body via wireless telemetry. Nerve-targeted FES systems often produce a more consistent, stronger contraction as they can recruit a larger volume of muscle tissue, can produce a more fatigue-resistant response, and allow for graded force production.^{6,11,12} Nerve stimulation electrodes cannot be used to target muscles that have been denervated due to primary motor neuron damage, though these muscles are often weaker and have much higher thresholds for stimulation regardless of technique. Additional discussion of electrode design is included in the Neural Recording section.

Standing and walking

While wheelchairs are capable of providing mobility to individuals with SCI, restoration of walking and standing is still a high priority for many people. Assisted or independent standing has many physiologic benefits in addition to practical considerations such as increasing accessibility.¹³ A lack of weight-bearing exercises like standing has also been linked to dramatically lower bone mineral densities in people with SCI, which can increase the risk of fracture.¹⁴ It should be noted that powered orthoses, or exoskeletons, are being developed to provide standing and walking functions to individuals with paraplegia, although those are beyond the scope of this manuscript. For a review see Ref.¹⁵ To date, only one FES walking system has received marketing approval from the FDA. The Sigmedics Parastep (Fairborn, OH) is a surface FES system that allows for up to six channels of stimulation of lower limb muscles.^{16,17} The system enables standing and walking through patterned muscle stimulation driven by switch modules on an instrumented walker. Surface stimulation systems can be limited due to high energy requirements, slow walking speed, and difficulty donning and doffing the system.^{5,18} An alternative approach is to use an implanted system. Implantation of indwelling electrodes

allows for more efficient muscle activation and greater force production and also removes the need to place surface electrodes.^{19,20} FES of the bilateral erector spinae, gluteus maximus, semimembranosus, and vastus lateralis has been demonstrated to provide functional rise-to-stand movements, sustained standing, and even slow walking when assisted by a walker or orthosis in individuals with thoracic level SCI.^{13,19} Unfortunately, loss of sensation after SCI makes balance and natural gait very difficult. Researchers have combined FES with orthoses in order to improve balance reducing the reduce the energy requirements placed on the user's arm.^{21–23} For a review of hybrid FES systems, see Ref.²⁴ There is currently no implantable FES system (with or without an orthosis) available commercially in the United States, although some devices are currently undergoing clinical trial. Work is

underway to optimize the coupling of the FES and orthoses and to create controllers that adapt to changing muscle properties and/or modify stimulation parameters as part of a closed-loop system.

Upper extremity

One of the most common goals of FES has been to reanimate the hand and arm in individuals with tetraplegia. In many cases, particularly for individuals with cervical SCI, upper arm function remains intact and only grasp is needed to increase independence in performing activities of daily living (ADLs). Many grasp variations can be achieved even through stimulation of surface electromyogram (EMG) electrodes. Fig. 1 shows an example of surface EMG electrodes (Fig. 1A), along with many other types of electrodes used for neural interfaces. Many surface FES systems for grasp have been

Figure 1 Example electrodes used in neural interface technology. (A) Delsys (Boston, MA) parallel bar surface electromyography (EMG) sensor. (B) Epimysial electrode (Ardiem Medical, Inc., Indiana, PA, USA). (C) Intramuscular electrode (Ardiem Medical, Inc.). (D) Nerve cuff electrode (Ardiem Medical, Inc.). (E) Utah slant array (Blackrock Microsystems, Salt Lake City, UT, USA). (F) Epidural spinal cord stimulation electrode (Boston Scientific, Natick, MA, USA). (G) Intraspinal microstimulation (ISMS) electrode (University of Alberta, CN). (H) High-density floating microelectrode array (MicroProbes for Life Science, Gaithersburg, MD, USA). (I) Electroencephalography (EEG) electrode cap. (J) Standard clinical electrocorticography (ECoG) array (top) and custom high-density ECoG array (bottom) (Ad-Tech Medical Instrument Corporation, Racine, WI, USA). (K) NeuroPort intracortical microelectrode array (Blackrock Microsystems).

developed and used in clinical trials including the Bionic Glove²⁵ (University of Alberta, Canada), Belgrade Grasping-Reaching System²⁶ (University of Toronto, Canada), ETHZ-ParaCare neuroprosthesis²⁷ (Zurich, Switzerland), and the NESS H200²⁸ (Bioness Inc., Valencia, CA, USA). The NESS H200 is currently the only commercially available surface-stimulation FES device for grasping. The device is marketed for both rehabilitation and daily use, and utilizes a remote-controlled switch to initiate and change between palmar and lateral grasps. For a review of FES grasp systems, see Ref.²⁹

Implanted FES systems eliminate the need to place electrodes daily and allow for more targeted stimulation. The FESMate (NEC Medical Systems, Tokyo, Japan) is a percutaneous FES system that can be used to stimulate muscles of the hand, arm, and shoulder based on command signals from switches, voice, sip and puff, or joysticks.³⁰ To our knowledge, no formal assessment of outcomes has been published.⁶ The Freehand system (NeuroControl, Cleveland, OH, USA) was the only commercial implanted FES system for grasp and was capable of both palmar and lateral grasp, although this device is no longer on the market. This device was based on the work of the Cleveland FES Center³¹ and was meant as a permanent tool to improve independence. A joystick on the contralateral shoulder is used to control the degree of hand opening. The system provided improved ADL independence in nearly all of the 250 individuals implanted.³² More recent work has focused on replacing the external shoulder position control with ipsilateral wrist position control as well as adding EMG-based control.³³ Unfortunately, in many cases denervation and lack of voluntary control of stabilizing musculature require extensive surgical intervention before these devices are useful.³⁴ Improvements will require more channels of stimulation, and the ability to effectively and efficiently stimulate larger muscles, both of which may be addressed by replacing the common epimysial and intramuscular electrodes (Fig. 1B and C) with peripheral nerve stimulating electrodes (Fig. 1D and E).^{11,35} More complex systems will be required to restore natural movement of the upper limb including dexterous grasp function and fine motor control. To make full use of these additional stimulation capabilities, improvements in command signals will be required (see Neural Recording section for additional details).

Trunk stabilization

Individuals with SCI in the high thoracic or cervical levels often suffer from paralysis of the core trunk

muscles leading to difficulty breathing, contracture, back pain, pressure ulcers and compromised organ function due to high internal pressures,⁵ as well as limited reach and difficulty with transfers due to poor balance.³⁶ Implantable FES electrodes have been used to stimulate the lumbar erector spinae (and other muscles) and demonstrated an improvement in posture, forward reach and effort required for transfers.^{19,37} Since trunk stabilization is desired anytime the user is not lying down, additional research is needed to develop a controller capable of stimulating tonically at levels that do not cause fatigue, and in closed-loop fashion using postural feedback to maintain balance during a variety of activities.³⁸ While stimulation of trunk muscles has standalone benefits, some individuals may also need trunk stabilization in order to take advantage of FES for walking or upper extremity function. Users may benefit from an integrated FES system that provides function to more than one part of the body.

Epidural and intraspinal microstimulation for locomotion

As stated above, restoration of walking is a priority for individuals with SCI. In addition to peripheral nerve and muscle stimulation with FES, direct activation of the spinal cord may hold potential for restoring locomotion. It has been recognized since some of the earliest investigations into the spinal cord that it functions as far more than simply a passive relay of signals between the brain and the periphery. Sherrington's early work into the nature of reflexes recognized the spinal cord as an integral component in the overall control and regulation of movement.³⁹ Central pattern generators (CPGs) that exist in the spinal cord are capable of producing rhythmic activity of the limbs without requiring any sensory feedback^{40,41} and also integrate supraspinal signals and sensory feedback to produce robust limb movement.⁴² Basic science research has demonstrated that this system remains functional after complete SCI, allowing cats to regain weight-bearing locomotion during treadmill walking.^{43,44} After SCI, however, a driving signal must be provided to the spinal cord either naturally via afferent activity resulting from leg movement on a treadmill or artificially by electrical stimulation. Two neuroprosthetic technologies that target the spinal cord directly are described here: epidural spinal cord stimulation and intraspinal microstimulation (ISMS; Fig. 1F and G). These neuroprostheses are unique in that they capitalize on spared spinal circuitry⁴⁵ rather than bypass it.

Epidural stimulation of the posterior aspects of the spinal cord through large electrodes placed on the dura mater is a technique that is used clinically to treat intractable pain⁴⁶ and as an investigational method to treat spasticity.⁴⁷ This technique may also be useful for activating CPGs for locomotion. The first clinical study of epidural stimulation for locomotion demonstrated that stimulation over lumbar segments of the spinal cord led to rhythmic alternating movement of the legs, providing strong evidence for the existence of excitable CPGs in people.⁴⁸ Since this demonstration, epidural spinal cord stimulation has been used in several clinical studies that have led to improved walking performance in people with incomplete SCI^{49–51} and in at least one person with a motor complete injury⁵² in conjunction with treadmill training. While epidural spinal cord stimulation to restore locomotion is far from an accepted clinical practice, the availability of clinical devices capable of delivering electrical stimulation makes it feasible to continue clinical testing of this approach. Since many questions remain about how to best deliver this stimulation, including optimal spinal levels and stimulation pulse parameters, further animal research will likely be used to guide clinical testing and development of improved systems.^{53,54}

ISMS as a neuroprosthetic technique was first investigated to restore bladder function after SCI,^{55–59} although results have been mixed and the small size of the target structures make this a challenging problem. Restoration of locomotion through ISMS has been pursued more aggressively.^{60–63} ISMS implants in these studies typically consist of arrays of up to 16–24 platinum-iridium microwires, 30 μm in diameter implanted into the lumbar enlargement and targeting hindlimb motoneuron pools in the ventral horn of the spinal cord. ISMS is capable of selectively activating muscles depending on which electrode is stimulated^{60,64} allowing for generation of specific movements and minimizing unwanted contractions of nearby muscles. Stimulation also acts through recruitment of afferent pathways in the spinal cord.⁶⁵ In cats, tonic stimulation with ISMS can generate locomotor-like activity⁶⁶ and can produce fatigue resistant muscle contractions.⁶⁷ While initial trials in people with SCI are on the horizon, several challenges remain including development of a multichannel stimulator and electrode array suitable for implantation in the human spinal cord and addressing safety issues associated with long-term microstimulation (see section on Intracortical Microstimulation). For both epidural and intraspinal spinal cord stimulation, further testing is also needed

to determine which injury levels and types (in terms of completeness) are most responsive to spinal cord stimulation. As previously discussed, muscles changes below the level of the lesion lead to weakness, poor balance, and fatigue. These factors will need to be accommodated through training or orthoses no matter which method of neural stimulation is used. Spinal cord stimulation could also be augmented with other forms of FES in order to stabilize the trunk.

Bladder neuroprostheses

Partial or complete loss of bladder control often occurs after SCI. Bladder dysfunction may manifest in several ways: an inability to retain urine in the bladder due to an overactive bladder or underactive sphincter (incontinence), an inability to completely empty the bladder (voiding dysfunction) and detrusor-sphincter dyssynergia when aberrant reflexes lead to concurrent bladder and sphincter contraction. Typical bladder management involves regular clean catheterization to empty the bladder and antimuscarinic drugs that reduce bladder overactivity. A failure to adequately manage bladder care can lead to infections and renal failure and has a significant negative impact on quality of life.

Individuals with SCI who do not respond well to medications or want to reduce their dependency on catheterization may benefit from bladder neuroprostheses.⁶⁸ In general, patients must have a bladder that can contract and intact motor nerves to the bladder to be eligible for these devices.⁶⁹ Two commercial bladder neuroprostheses are available to patients with non-neurogenic bladder dysfunction, who have intact spinal reflex circuits that control the bladder. The Medtronic Interstim (Minneapolis, MN, USA) promotes continence and improved bladder function through extradural stimulation of a sacral nerve root although the neuromodulatory mechanisms are unclear. Off-label studies of Interstim devices in people with chronic SCI have shown limited success as they are more effective for individuals with an intact spinal cord and non-neurogenic bladder dysfunction.⁷⁰ Recent results, however, suggest that early implantation of the Interstim, within a few months after SCI, may provide significant benefits.⁷¹ The mechanisms driving these potential benefits are not well understood and are being investigated in SCI animal models. The Uroplasty Urgent PC stimulator (Minnetonka, MN, USA) is another commercially available bladder neuroprosthesis.⁷² In this device, percutaneous wire electrodes are inserted near the tibial nerve in the foot during weekly stimulation sessions to activate sacral spinal circuits which mediate continence reflexes.⁷³ To date, few

studies have investigated this approach in patients with SCI^{74,75} indicating the need for further study in this patient population.

The primary device available to patients with SCI is the Brindley-Finotech sacral anterior root stimulator (Finotech Medical, Welwyn Garden City, UK). While widely used in Europe, this device is not currently commercially available in the United States. Electrical stimulation controlled by an implanted pacemaker-like device drives the bladder and the urethral sphincter. Intermittent stimulation patterns are used to allow bladder emptying during stimulation off-periods when the somatic sphincter relaxes before the bladder, leading to bladder emptying in spurts.⁶⁹ While this device improves quality of life,⁷⁶ a dorsal sacral rhizotomy is often required to eliminate undesirable reflex sphincter and bladder contractions.⁶⁹ The rhizotomy eliminates other pelvic reflexes and is not well received by patients.⁷⁷ High-frequency (HF) nerve block of the sphincter may eliminate the need for a rhizotomy⁷⁸ and be more acceptable to patients.⁷⁷ Another approach for eliminating undesirable reflex sphincter contractions may be non-invasive stimulation of sacral dermatomes, which has shown potential in acute⁷⁹ and chronic⁸⁰ SCI cats.

An alternate approach gaining traction in recent years is the stimulation of afferent pudendal nerve pathways for reflex bladder control for patients who have intact spinal circuits that control the bladder. Afferent pudendal stimulation may not require a rhizotomy,⁸¹ necessitates less time for surgical implantation than sacral root stimulation,⁸² and may be beneficial for both neurogenic and non-neurogenic bladders. Electrical or mechanical stimulation of the distal genital pudendal branch has been well established to lead to bladder relaxation and continence in intact and SCI cats⁸³ as well as patients with SCI⁸⁴ primarily in short-term studies. In one study comparing pudendal nerve stimulation to sacral root stimulation, a majority of patients with non-neurogenic bladders preferred the pudendal nerve approach.⁸² Flow receptors in the urethra are thought to mediate a micturition reflex, which can be triggered by stimulating the pudendal nerve trunk or branches to the urethra while the bladder is partially full. Studies in cats have established that specific stimulation patterns may be optimal for selection of the pudendal-mediated continence and micturition reflexes.^{83,85,86} Studies in humans, with intraurethral⁸⁷ and percutaneous pudendal⁸⁸ stimulation approaches support the potential for this approach. As the pudendal nerve provides somatic control of the sphincter, selective stimulation of the desired pudendal afferent pathways⁸⁹

or HF nerve block of the sphincter⁹⁰ are critical to the success of this approach.

Bladder dysfunction remains a significant issue after SCI. As yet, no neural interface offers complete bladder control without some undesirable side effects. Individuals with SCI have indicated that potential side effects would be the most significant factor for choosing a neural prosthesis for bladder function.⁷⁷

Modifications to the Brindley approach, such as including HF nerve block or dermatome stimulation, or continued advancement of the pudendal nerve approach hold promise for restoring control for individuals with SCI.

Intracortical microstimulation to restore sensation

Electrical stimulation through microelectrodes implanted in the cortex (Fig. 1H), or intracortical microstimulation (ICMS), has been proposed as a method to restore a variety of sensory functions by activating neurons that would normally be responsive to a now disconnected sensory input. ICMS is still in the early phases of preclinical testing in terms of the ability to convey sensory information so many of the possible applications remain speculative at this point. One possible application of ICMS would be providing relevant sensory signals including tactile and proprioceptive sensations from an FES controlled limb or robotic prosthesis under direct brain control. Perhaps more medically relevant would be transmitting bladder distention signals or pain and pressure signals from deep muscle tissue. Knowledge of these lost peripheral sensations could enable patients to make decisions about when to empty their bladder or when to change their posture to prevent pressure sore formation. These applications have not yet been investigated. An intracortical implant would not be necessary for conveying information about simple bladder or pain signals. However, if ICMS was already being used to convey more complex information related to upper limb movement, information about these visceral sensations would be a valuable supplement.

The loss of proprioception and tactile cues may make it more challenging for people with SCI to take advantage of neuroprosthetic technology designed to restore movement, as well as external assistive technology like exoskeletons and robotic manipulators. Proprioception is generally considered to be crucially involved in the learning and control of motor action and loss of proprioception can have a significant effect on a person's ability to move without visual input.^{91,92} ICMS studies of proprioception are complicated by the location of area 3a (primary receiving area of proprioceptive

information) deep in the central sulcus, making access to this area with high-density electrode arrays challenging. Also, neurons in area 2 (another area with proprioceptive functions) of primary somatosensory cortex are known to have complex receptive fields making it difficult to deliver precise feedback via cortical stimulation.⁹³ However, recent animal research is beginning to address these questions of how proprioceptive feedback may improve BCI prosthetic control⁹⁴ and how artificial proprioception might be delivered through ICMS.⁹⁵ While studying proprioception is particularly challenging, a great deal more is known about the structure and function of the cutaneous areas (3b and 1) of somatosensory cortex. Non-human primates can distinguish between different ICMS frequencies at the same performance level as a mechanical task in which different levels of vibrotactile stimulation were applied to the finger.⁹⁶ This work demonstrated that information transmitted to the brain by ICMS could be used as well as natural sensory inputs to make decisions. Recent experiments involving ICMS of tactile regions of the brain are also beginning to demonstrate its utility in the context of BCI control.^{97–99}

Despite the potential usefulness of ICMS to provide valuable sensation to patients, very little clinical work has been done. The only published clinical ICMS work comes from two reports where ICMS in visual cortex was used to elicit phosphenes in people with chronic blindness.^{100,101} In addition to some of the scientific barriers to ICMS, many technical barriers also exist. The current densities associated with ICMS are much higher than those for large electrodes such as deep brain stimulation devices, which has led to concerns about the long-term reliability of the electrodes and the safety of the tissue around the electrode although histological analysis of the local tissue site has provided mixed results.^{102,103} Special electrode coatings can increase the amount of charge that can be injected while minimizing the damage done to the local surrounding tissue.^{104–109} A further challenge is the development of high-channel count stimulators, which currently only exist in research labs.¹¹⁰ ICMS has the potential to drive very high-resolution sensory signals directly into the brain, and although clinical experiments using this technology will rapidly push the field forward, it is likely that it will be many years before this approach will be used regularly in a clinical setting.

Neural recording interfaces for command and control

The neurostimulation devices described above attempt to restore function or provide sensory feedback to

people with SCI. Commands for these devices are usually derived from mechanical interfaces such as switches or joysticks. As assistive technology continues to progress to provide more natural and complex functions, it is important to develop robust and intuitive command signals. These signals may come from muscles, nerves, or even directly from the brain. Further, by recording information about limb-state or bladder pressure, it may be possible to close the loop between the neurostimulation technology and the user in order to improve performance.

Recording interfaces to measure residual muscle or nerve activity

For individuals with residual motor function, muscles or nerves may provide an intuitive control signal for devices like FES. However, finding robust and accurate volitional command signals for assistive devices is particularly challenging in the SCI population. In some cases it is necessary to extract commands from muscles in the face or neck or from muscles weakened by paralysis. Many techniques have been used to record volitionally modulated electrical activity in muscles (EMG) and nerves (electroneurogram, ENG). EMG recording techniques include surface electrodes on the skin, epimysial electrodes that are attached directly to the muscle, and intramuscular fine wire electrodes (Fig. 1A–C). These electrodes have been used both on a temporary basis (e.g. for a trial period prior to full implantation) as well as chronically in clinical applications.^{13,23,33} EMG-based commands have also been studied for controlling hand grasp FES. While specialized instrumentation is required to record these signals reliably, it can provide an intuitive and robust control signal when residual muscle activity is present.³³ Unfortunately the number of potential independent EMG signals under voluntary control can be fundamentally limited.

For ENG, peripheral nerve cuffs and penetrating electrode arrays have been investigated (Fig. 1D and E). Small signal levels and low selectivity can limit the resolution of nerve cuffs which have been tested in humans.^{111–113} Without proper precautions, ENG signals may be contaminated with EMG interference from surrounding muscles limiting clinical utility. To improve the performance of nerve cuffs, increases in the number of electrode channels,¹¹⁴ changes in cuff geometry to bring nerve fascicles closer to electrodes¹¹⁵ and advances in signal processing to enhance signal source discrimination¹¹⁶ are all being investigated. Neural recording interfaces that penetrate the perineurium yield greater selectivity of individual

afferent fibers by placing electrodes within or next to fascicles. Longitudinal intrafascicular electrodes (LIFEs) have several electrode channels that are threaded into peripheral nerves. LIFE recordings of single afferents in the tibial and peroneal nerves can lead to accurate estimates of the ankle joint angle.¹¹⁷ The Utah slant electrode array (USEA) provides greater selectivity by targeting all fascicles in a nerve with a grid of up to one hundred electrode channels inserted transversely (Fig. 1E).¹¹⁸ Limitations of the USEA include signal contamination from muscle activity, rigidity of the implant and a degradation of neural signal quality over time, although improvements have been demonstrated recently.¹¹⁹ Penetrating electrode arrays may offer additional advantages including the possibility of recording multiple independent commands from a single array of implanted electrodes.^{116,120,121}

Because of paralysis and weakness after SCI, EMG and ENG-based control may require the user to learn a new and often unnatural strategy to command FES stimulation. The muscles or movements chosen as actuators are often functionally and anatomically unrelated to the muscle(s) they control in order to avoid complications with coupling during use. EMG and ENG techniques hold special promise for those with incomplete SCI since in these cases it may be possible to stimulate a given muscle based on its own EMG signal. In many cases even when an injury is functionally motor complete, a small amount of nerve fibers survive.¹²² Making use of EMG or ENG signals from the target muscle/nerve itself is an active area of research as an FES command signal that would provide a more intuitive control scheme.

Brain–computer interfaces

BCIs are an alternative command source for assistive technologies for people with significant paralysis who are unable to use traditional interfaces, like joysticks, or muscle-derived control strategies. A BCI records neural signals and decodes a user's intention to operate a device and also provides feedback to the user about their brain activity. This feedback could be visual, like the movement of a computer cursor, auditory, or even tactile. Various sensors, including electroencephalography (EEG, Fig. 1I), electrocorticography (ECoG, Fig. 1J), and intracortical microelectrodes (Fig. 1K), can be used to record neural activity from the brain. Differences in signal quality and stability, invasiveness, and system complexity can all influence the choice of electrode type.

EEG-based brain–computer interfaces

EEG records signals that represent the sum of electrical activity generated primarily by postsynaptic currents of neurons in the vicinity of a large electrode on the scalp surface. EEG is non-invasive and has a long history of human testing.¹²³ Until recently BCIs have been used primarily in a research setting. However, a few EEG-based BCIs, such as the Intendix (g.tec, Graz, Austria), are now on the market for in-home use for computer access, to operate electronic spellers, or to interface with environmental control units.

Most EEG-based BCI technology is focused on either making selections or moving devices.^{124,125} The goal of selection systems is to allow individuals to select items such as in a computer menu or letters on a keyboard and typically rely on evoked potentials resulting from attention to visual stimuli.^{126–128} EEG systems have also been developed to control the movement of devices such as a computer cursor, wheelchair, robotic arm, or an upper-extremity FES system. Typically motor-related EEG signals are used to control these movement-systems to provide a more intuitive mapping between brain activity and device output. Characteristic changes in mu (8–12 Hz) and beta (18–26 Hz) band activity related to movement¹²³ can still be observed in individuals years after SCI.^{129–131} EEG-BCIs have been used to achieve 2D and 3D computer cursor control^{132,133} and simple control of FES hand-grasp systems.¹³⁴

Although EEG has proven useful for commanding simple assistive devices, the information that EEG conveys is often broad and non-specific due to attenuation of the neural signal as it passes through the skull.^{123,135} This leads to limitations on the number of degrees-of-freedom that can be controlled using EEG and how intuitive the commands can be, even with the use of advanced spatial filtering.¹³⁶ However, EEG-based commands could be used to supplement other volitional activity, such as residual muscle activity, in a hybrid system that can provide higher degree-of-freedom systems^{137,138} for individuals not willing to undergo electrode implantation surgery. Another limitation of EEG is the need for caretaker assistance in donning and doffing scalp electrodes on a daily or more frequent basis. In addition, the aesthetics of electrodes and wires on an individual's head can be undesirable. A fully implanted subdermal system may help alleviate these negative aspects.

ECoG and intracortical microelectrode BCIs

High degree-of-freedom neural control signals will be required in order to restore complex and natural

movement using FES or powered orthoses, particularly of the upper limb. Implanted electrodes record more detailed information from the cortex than surface electrodes due to higher spatial resolution and proximity to the neural sources. ECoG uses electrodes placed directly on the surface of the brain to record electrical activity from the cortex. ECoG preserves the gamma band (40–200 Hz) component of the electrical field potentials which has been shown to carry movement information such as direction of movement,^{139,140} finger kinematics,^{141–143} and hand posture.^{144,145} Typically ECoG is used for mapping seizure foci and eloquent cortical areas in patients with intractable epilepsy prior to surgical resection of cortical tissue, although limited trials of ECoG BCI have been conducted in people with SCI and other motor impairments.^{146–148} Some of these studies have used custom ECoG electrodes with smaller diameter electrodes and closer electrode spacing that maximize the spatial resolution and provide an even richer neural signal for BCI control (Fig. 1J). Recently, an individual with C4 complete tetraplegia used an ECoG BCI to control a computer cursor and robotic arm in three-dimensions.¹⁴⁶ Since ECoG records from the surface of the brain, it is thought that the signal may be more robust over time than intracortical recordings although longer-term studies are needed. Non-human primate studies suggest that ECoG carries significant movement-related information that is stable over at least one month.^{149,150}

Another type of implanted electrode, typically called an intracortical microelectrode, penetrates a small distance into the cerebral cortex and can record activity from single neurons. Intracortical electrodes are typically 10–50 μm in diameter, 1–5 mm in length, and manufactured as arrays that allow for recording of many neurons simultaneously.¹⁵¹ These electrodes connect to a percutaneous connector that attaches to the skull. Limited clinical trials of these devices have occurred in individuals with tetraplegia.^{152–154} Animal and human studies have shown that detailed movement-related information can be extracted from the motor cortex and use to control assistive devices such as robotic arms^{153–156} or FES systems.^{157,158} Over time, the microelectrodes can become encapsulated by a glial scar that leads to a decline in signal quality. However, some studies have shown that recordings can last for more than 5 years.¹⁵⁹ Researchers are working to combat this encapsulation problem through innovative electrode geometry, materials, and coatings.^{151,160–163} Molecular strategies include using neurotrophic factors and/or modulated drug-delivery to reduce the foreign body response.^{164–166} In order for intracortical electrodes to

become a viable clinical BCI option where patients may need to use the device for decades, the robustness and longevity of recordings needs to be improved.

Drawbacks of ECoG and intracortical BCIs include required implantation surgery, cost, and increased system complexity.¹⁶⁷ In order to make implanted BCIs available for widespread clinical use, additional technical development is needed. Currently, researchers are working to improve the chronic recording quality for these implanted sensors and also to develop fully-implantable wireless systems.^{168–170} Implanted systems will reduce the risk of infection as well as noise that can contaminate the signal as it is communicated via transcutaneous wires. Transcutaneous wires are susceptible to breakage and this risk could be eliminated by a fully implantable system. Further, an implanted system would improve the aesthetics of the BCI. Researchers are working with transcutaneous systems to determine how much information needs to be transmitted to effectively control a complicated end effector, which will dictate data transmission and power requirements for implantable systems.

Patients, physicians, and assistive technology specialists will need to work together to determine which control interface is most appropriate. A balance between performance and potential risk will need to be evaluated when choosing a system. BCIs are likely to be appropriate for people with very limited mobility who desire control of complex assistive technology. People with SCI have indicated that being able to operate a BCI independently is the most desirable feature.³ Most the people surveyed indicated that non-invasiveness was a very important design characteristic, however more than half indicated that they would definitely, or very likely, consider having surgery to implant BCI electrodes. In addition to non-invasiveness, daily-setup time, independent operation, cost, number of functions provided, and response time were all considered very important design characteristics for a BCI. Users placed a lower priority on the initial training time required to learn to use the device, but the amount of interventions and retraining should be minimized. Pre-clinical and clinical studies are currently being conducted that will start to establish baseline performance and risk profiles for each type of device.

Sensory neural recording interfaces to monitor bladder and limb-state

Monitoring the state of limbs and internal organs has long been a goal in neuroprosthetics. Individuals with SCI often lose sensations from the limbs such as proprioception, touch and pain as well as from the

bladder. These individuals are unable to move their limbs effectively, may be unaware of a peripheral injury, and do not notice when their bladder is full. Neural recording interfaces that monitor these sensations can help individuals regain lost function.

The bladder neuroprostheses described above do not incorporate sensory feedback, however, by closing the loop between sensory input and stimulation output, it may be possible to improve device performance. Sensory recordings could inform the user when the bladder is full to ensure that voiding is performed in a timely manner. Similarly, sensory recordings could sense when voiding was complete to prevent a patient from turning it off too soon, or forgetting to turn it off. For the interstim or pudendal nerve approaches described above, sensory recordings could allow for conditional stimulation only when it is needed or to modulate the stimulation parameters to match the bladder state. Nerve cuff recordings from a sacral spinal nerve root¹¹¹ and on the pudendal nerve¹⁷¹ can detect bladder contractions. In these applications, gross changes in the bladder pressure or reflexive closure of the sphincter are detected from the aggregate activity of many individual afferent fibers. Closed-loop control may help improve bladder neuroprostheses to reduce potential side effects and improve effectiveness for continence and voiding which are the two most important design characteristics to consumers.⁷⁷

As described above, FES is one approach to restoring motor function. FES is normally performed in an open loop mode, with stimulation patterns applied to muscles or nerves in a fixed pattern and duration without respect to the current state of the target limb. While FES can restore function, perturbations and muscle fatigue limit effectiveness. There is a growing effort to incorporate sensory feedback in FES control. Sensory recording interfaces with peripheral nerves have several advantages over external sensors, including integration with natural body sensors, a reduced obtrusiveness and a limited need to reposition.¹⁷² Nerve cuffs on the sural nerve and the palmar digital nerve have been used to detect foot contact and finger touch for closed loop FES control of foot dorsiflexion¹¹³ and hand grasp.¹¹² Nerve cuffs and penetrating electrodes that target peripheral nerves are limited to signals from a single joint, skin region, or part of an organ and must reject motor signals. For monitoring multi-joint limb movements or obtaining a greater resolution of bladder activity, it may be necessary to target nerve trunks and to use specially designed electrodes that allow access to diverse nerve fibers within a single nerve bundle.

In recent years, dorsal root ganglia (DRG) have gained attention as a source of sensory signals. The convergence of fibers at the DRG may address some of the peripheral interface challenges. Recordings with penetrating electrodes, such as a Utah electrode array, in one or two DRG can give accurate state estimates of an entire limb^{173,174} and be used as sensory feedback in closed-loop control of FES for locomotion.¹⁷⁵ Also, high-resolution sensory signals from the bladder, urethra and other structures of the pelvis can be obtained with sacral DRG neural recording interfaces.¹⁷⁶ DRG interfaces with penetrating electrodes require a challenging placement near the spinal cord and have yet to demonstrate effective long-term recordings.¹⁷³ Non-penetrating neural interfaces with the DRG may alleviate these concerns by yielding selective recordings at the surface, as afferent cell bodies are packed below the DRG perineurium.¹⁷⁷ This less-invasive approach may offer a quicker path to human evaluations while offering a signal quality that approaches neural signals recorded with penetrating electrodes.

Peripheral recording interfaces may be useful for obtaining body-state feedback signals that would be useful for restoring control of functions lost after SCI. Although only limited studies have been performed in humans, improvements in the technology and investigations of new anatomical targets should lead to useful applications in the near future. Further study is needed to determine whether closed-loop control of neuroprosthetics offers improved performance and embodiment of assistive devices.

Conclusions

Neuroprosthetics hold great potential for restoring function and sensation for people with SCI. Improvements in robustness, longevity, and effectiveness will lead to devices that are capable of meeting the priorities of the SCI population. Another important ingredient for clinical translation is to include the users in the design and evaluation process. This will not only serve to direct the research and preclinical evaluations, but it has been documented that consumers who feel more informed about assistive technology are more satisfied with their device.¹⁷⁸ The devices discussed in this manuscript attempt to restore function to the user's own limbs or organs, which is a highly desired characteristic of neuroprosthetic technology. Combining neural stimulation and recording technologies may result in intuitively controlled assistive devices that address the needs of the population with SCI.

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