# Title: Spinal Cord Bioelectronic Interfaces: Opportunities in Neural Recording and Clinical Challenges

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## Abstract

Bioelectronic stimulation of the spinal cord has demonstrated significant progress in the restoration of motor function in spinal cord injury (SCI). The proximal, uninjured spinal cord presents a viable target for the recording and generation of control signals to drive targeted stimulation. Signals have been directly recorded from the spinal cord in behaving animals and correlated with limb kinematics. Advances in flexible materials, electrode impedance and signal analysis will allow spinal cord recording (SCR) to be used in next-generation neuroprosthetics. In this review, we summarize the technological advances enabling progress in SCR and describe systematically the clinical challenges facing spinal cord bioelectronic interfaces and potential solutions, from device manufacture, surgical implantation to chronic effects of foreign body reaction and stress-strain mismatches between electrodes and neural tissue. Finally, we establish our vision of bi-directional closed-loop spinal cord bioelectronic bypass interfaces that enable the communication of disrupted sensory signals and restoration of motor function in SCI.

## 1.1 Introduction

Spinal cord injury (SCI) is an acute disabling condition resulting from the disruption of neurological pathways between the brain and the peripheral nervous system, which can lead to irreversible loss of motor and sensory function in severe cases. SCI is estimated to affect 250 000 to 500 000 individuals annually[1], preferentially affecting young adults at their peak of occupational productivity with estimated lifetime costs ranging from $1.1 to $4.5 million US dollars[2]. Apart from the economic burden, individuals with SCI are profoundly affected by the loss of motor, autonomic and sexual function, with variability in their priorities for recovery based on the severity and chronicity of their injuries[3–5].

Despite recent advances in neuroprotective and cell-based therapies in the exploratory management of motor function loss in SCI, these strategies have yet to demonstrate consistent clinical outcomes[6,7]. Readers are referred to comprehensive reviews in these fields by Onose et al[8] and Fan et al[6] as the focus of this review is on bioelectronic strategies in SCI. Neural bioelectronic devices

provide an alternative approach that enables the recording of electrical signals generated by neuronal depolarization activity or the activation of functional neural structures via electrical stimulation. By epidural stimulation of functionally intact spinal networks distal to the site of injury, this technology has been able to restore ambulatory function in human pilot trials[9–11]. Likewise, these devices can interpret electrical signals generated by the user's brain cortical activity to direct robotic devices[12] or enable functional muscle activation[13]. These neural signals can also be recorded from the spinal cord above the site of injury, which may represent an advantageous site given that volitional motor intent from the brain is processed via multiple circuits before descending in the spinal cord.

The recording of neural signals is also an important tool in neuroscience to study the connectivity of cortical processes, spinal networks and peripheral nerve conduction. Electrophysiology has progressed from the pivotal muscle reanimation studies described by Galvani[14] in the 18th century to novel electrodes enabling wide-scale recording of brain activity[15], expanding our understanding of neural connectivity. This has resulted in the translation of electrophysiology in widespread clinical use, ranging from the diagnosis of epilepsy[16–18], nerve conduction disorders[19] to real-time intra-operative neuromonitoring, allowing surgeons to safely perform complex cranial[20,21] and spinal surgery[22,23].

Whilst cortical brain and peripheral nerve electrophysiological recordings have been studied extensively, recording motor and sensory signals from the spinal cord is only gaining traction in the recent decade with improvements in electrode technology and signal processing methods. The proximal, uninjured spinal cord is a logical target when designing bioelectronic devices that can record motor volition as control signals for powering the patient's motor units or external assistive devices. As such, we aim to describe the differences between cortical brain and spinal cord recording (SCR), focusing on the advantages of recording signals directly from the spinal cord in applying neuroprosthetics to SCI management. We will then review the recent advances in SCR, partitioning our analysis into the motor and sensory decoding opportunities offered by SCR, as well as foundational developments in the field of electrophysiology and neuromonitoring. Our review will then focus on the clinical challenges facing SCR in neuroprosthetics, progressing systematically from design to implantation to post-operative surveillance. For each of the challenges, we have provided potential solutions based on current advances in electrode design, surgical implantation and modulation of chronic foreign body responses. We conclude with a vision for a chronic SCR device that can be potentially deployed to achieve a functional, bi-directional bioelectronic bypass in SCI.

## 1.2 Fundamentals of bioelectronic neural interfaces

Neurons typically comprise of dendrites, cell bodies and axons. In particular, axons serve an important function in the motor pathway, projecting from upper motor neurons to lower motor neurons located in the brainstem and spinal cord, which further project axons to the effector muscles to produce movement[24]. Neurons, with their projecting axons, can perform these specialized functions due to the electrical excitability of their selectively permeable bilipid layer membrane embedded with ion channels that activate in response to changes in electrical activity. The activation of these voltage-gated ion channels leads to changes in the membrane electrical potential, otherwise known as action potentials[25] (AP). It has been demonstrated that the generation of APs lead to transient changes in both extracellular and intracellular electrical potentials in the pioneering studies performed by Alan Hodgkin and Andrew Huxley[26].

Understanding of the underlying electrophysiological mechanism of nerve conduction has advanced since then, facilitated by techniques such as patch-clamp electrophysiology allowing investigation of individual ion channels[27] as well as multiple unit recordings sampling populations of neurons[28]. These advances in electrophysiological techniques were accompanied by developments in the analysis of data collected from recording neuronal activity, such as in the prediction of limb movement and trajectory from single neuron recordings as demonstrated in the classic primate centre-out task described by Georgopoulos et al[29].

Our understanding of the fundamental conduction pathways between the premotor areas in the cortex to the neuromuscular junction has been coupled with advances in electrode fabrication. These electrodes can be classified according to their level of invasiveness[30], the anatomical location along the conduction pathway at which they are deployed and whether they serve a primary stimulating or recording function[31]. The level of invasiveness is a clinically relevant method of classification as it relates to the surgical risk that a patient will experience with the implantation of the electrode device, the potential for acute and chronic neural injury and also the selectivity of neural signal recording and stimulation[32]. Invasiveness can be categorized broadly by the anatomical barriers in the way of the neural interfaces, with intraparenchymal devices penetrating the parenchyma to directly sample populations of neurons, followed by perineural interfaces which can be deep or superficial to the dura/epineurium and lastly surface electrodes in which signals are further attenuated by surrounding bony structures, connective tissue and skin[32]. The concept of invasiveness can be applied to both central (CNS) and peripheral nervous system (PNS) interfaces: surface interfaces can record cortical local field potentials via electroencephalography (EEG) and peripheral nerve action potentials via electroneurography (ENG); more invasive devices allow perineural recordings via electrocorticography (ECoG) in the brain and nerve cuffs in the PNS; and, at the most invasive of the spectrum, intraparenchymal devices such as microelectrode arrays (MEAs) for the CNS and PNS.

**Surface electrodes**

Surface electrophysiological recording methods allow for the least invasive means of recording neural signals and pose minimal risk of neural tissue injury. However, because of the layers of tissue (bone, connective tissue, skin) that the neural signals have to traverse before they are received by the electrodes, the signals are characterized by a high proportion of noise[33], assessed by the signal-to-noise ratio (SNR). In addition, the tissues attenuate high-frequency signals, limiting the analysis of EEG to low-frequency activities[34]. It is believed that the low-frequency signals captured by EEG reflect volume-conducted temporally summated synaptic activity in the cortex termed local field potentials (LFPs), although the origin and locality of these signals remain a source of debate[35]. The intrinsic low-pass filtering observed in EEGs mean that high-frequency signals from groups of neurons may not be reliably captured. Additionally, the spatial resolution of EEG is limited and spatial filters are required to enhance focal activity. Despite these limitations, EEG decoding has been able to decode motor cortical signals which are then fed into a functional electrical stimulation (FES) system targeting lower limb muscles to recreate the firing seen in a gait cycle, allowing a non-invasive neurorehabilitation system to improve motor outcomes in individuals with paralysis[13]. This pilot study necessitated an extensive period of rehabilitation according to a strict training protocol over 2 years and further trials are required to demonstrate if EEG decoding of motor signals is robust enough when applied to a larger population.

**Epidural and subdural electrodes (Invasive, non-penetrating)**

The dura is a protective tissue layer encasing the central nervous system in a bath of cerebrospinal fluid. Electrodes that are placed either epidural or subdural provides close-proximity interfacing with the underlying neural tissue, allowing for superior SNR and higher spatial resolution at the cost of increased invasiveness of the procedure. In the brain, electrocorticography (ECoG) devices were first used to localize epileptic seizures[18] but have since been applied as a brain-machine interface (BMI), demonstrating the ability to record motor cortical activity[29,36–38]. ECoG devices, by virtue of their extra-neural placement, elicit a lower biological response than intraparenchymal devices, allowing for safer chronic implantation of the electrodes[32]. When comparing extradural versus subdural implantations, the conductivity of the cerebrospinal fluid (CSF)[39] and dura[40] should be modelled prior to in vivo studies as this will affect the quality and selectivity of neural recordings. This is especially pertinent when designing spinal cord devices as the relative volume of the CSF is greater[41] and is subject to dynamic changes from vascular pulsations[42] as well as eccentric positioning of the spinal cord in the subarachnoid space[43].

**Intraparenchymal electrodes**

The use of intraparenchymal devices in the recording of cortical signals allows for the highest spatial selectivity, enabling the decoding of activity generated by populations of neurons in the brain as well as action potential spikes generated by multiple or single units[34]. The enhanced resolution comes at the cost of perineural injury as well as the chronic inflammatory response termed the foreign body reaction (FBR) (see **Biological Reactions**). The Utah Intracortical Electrode Array[44] is currently the only BMI approved by the United States Food and Drug Administration (FDA), allowing the control of a robotic arm using cortical signals[45] as well as high-performance brain-to-text communication[46] with demonstration of chronic interfacing at over 5 years[47]. Intraparenchymal electrodes have also been applied to the peripheral nerves in devices such as the Utah Slanted Electrode Arrays[48] and transverse intrafascicular multichannel electrodes[49] as well as the spinal cord, although there are specific mechanical challenges that have to be addressed before clinical use (see **Material Considerations**).

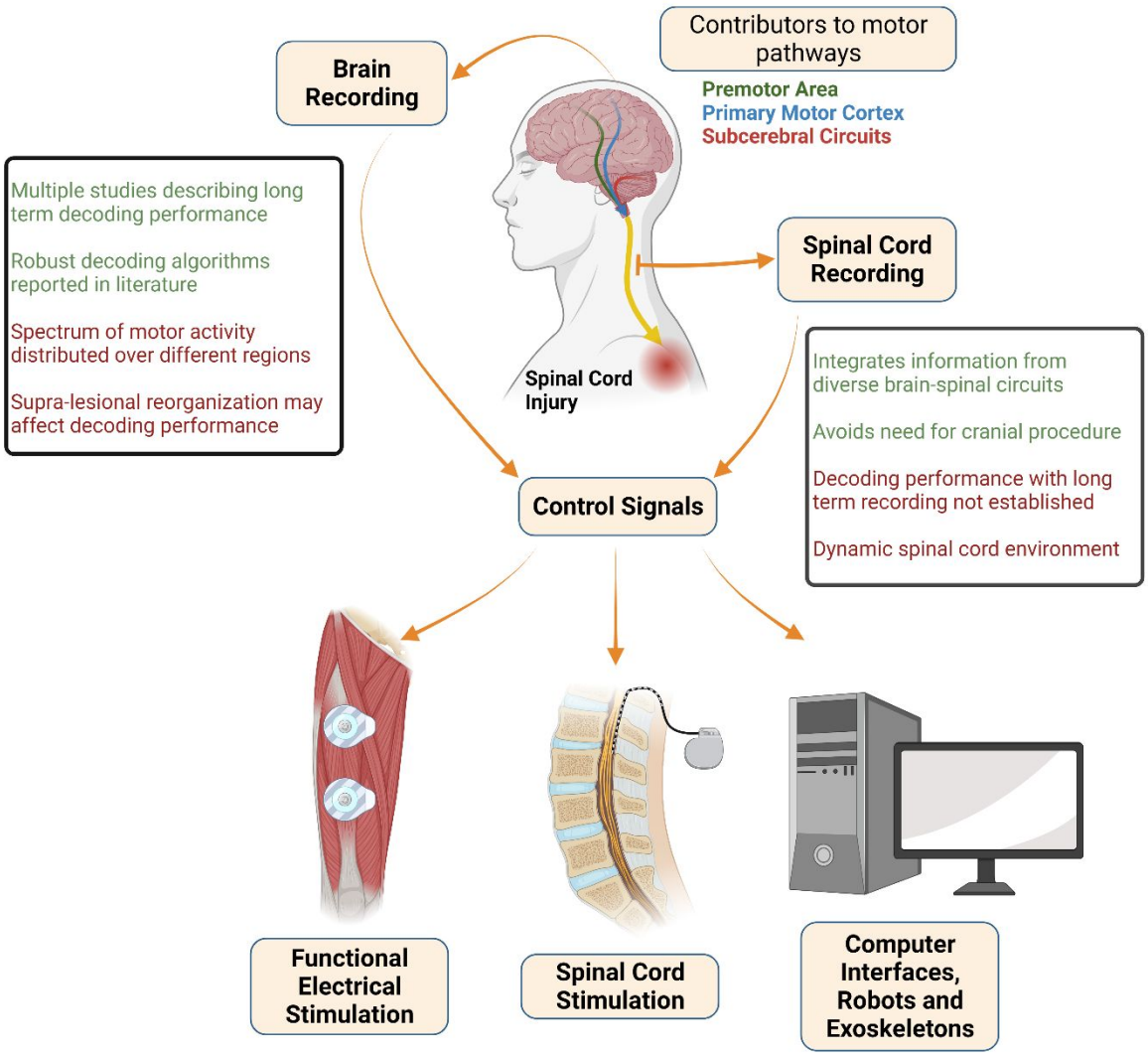


*Figure 1: Comparison between cortical and spinal cord recording. Both spinal cord and cortical recordings can be decoded to provide control signals for functional electrical stimulation, spinal cord stimulation or external devices. Spinal cord recording has the potential to record motor intent directly from the spinal cord which integrates motor information from various regions of cortical processing and modulation. Features of cortical versus spinal cord recording are highlighted and further explained in section 2.1. Created with BioRender.com.*

## 2.1 Comparison between cortical and spinal cord recording

Whilst motor decoding has been established with cortical interfaces, decoding motor and sensory signals from the spinal cord is emerging as an alternative target or adjunct for emerging neuroprosthetics. Although chronic recording from the motor cortical areas have been established in human trials, there are inherent biological and technological challenges in providing consistent chronic recordings from the brain (Fig. 1). Firstly, motor activity is represented over a wide area of the cortex, characterized by the phenomenon of fractured somatotopy[50] in which representations of motor activity are not discretely organized but are instead interspersed across different cortical regions. This means that recording cortical motor activity limited to the traditional motor and premotor cortical areas may not capture the full spectrum of volitional motor activity as described by the distributed-coding principle[51].

Secondly, cortical motor topography following SCI is characterized by dynamic processes in which cortical areas representing a specific motor function adapt to injury and reorganize[52–54]. This could lead to possible variations in the decoding abilities of brain-machine interfaces sampling the activity of a limited population of neurons over time following SCI. These limitations can theoretically be addressed with more extensive brain-machine interfaces allowing near whole-brain sampling, but an increase in the extent of sampling and device implantation would lead to attendant risks of intracranial haemorrhage, infection and introducing seizure foci[55]. These concerns regarding the risks of neurosurgery are reflected in a survey of individuals with paralysis[5], in which half of the participants would avoid having intracranial electrodes. This risk of iatrogenic injury above the injury site similarly applies to the spinal cord and thus the risk-benefit analysis in the selection of spinal cord recording level will be crucial, as the potential motor loss with complications arising from a cervical spinal cord level implant exceeds that of a thoracic level implant.

The concerns of undergoing intracranial surgery are especially relevant in individuals with SCI where the site of injury is at the spinal cord and not their brain. Recording motor and sensory signals directly from the spinal cord thus presents an alternative target for these individuals. From a systems neuroscience perspective, the spinal cord receives complex motor volition integrating abstract planning from the frontal and posterior parietal cortex[56], motor sequencing in the premotor area[57], filtering by the basal ganglia pathways[58] and finally to the primary motor cortex[50]. The motor signals from the primary motor cortex are then transmitted to the corticospinal, reticulospinal[59] and rubrospinal tract[60], with the former being the dominant motor tract in humans. Sampling directly from the spinal cord thus bypasses the complex architecture of the motor planning pathway and in an anatomical structure more densely represented by motor volitional signals, albeit also with closely located sources of noise such as autonomic and sensory signals. Additionally, the sensorimotor signals transmitted by the major tracts are located more peripherally in the white matter of the spinal cord compared to the grey matter, potentially allowing the recording of compound action potentials without deep implantation of electrodes.

Cortical decoding of motor intent, on the other hand, benefits from a longer history of experimentation with both penetrating[34] and non-penetrating[61] electrodes. Various algorithms for cortical motor decoding have been developed, including strategies that can adapt to neural control mapping changes after learning for more predictive chronic decoding[62]. These adaptive decoding algorithms are particularly useful as supra-lesional reorganization occurs throughout the brain and spinal cord following SCI[53]. Spinal cord recording, in comparison, had a shorter runway of development and is only just starting to make the leap from animal models to pilot clinical studies[63], with specific algorithms developed to improve the accuracy and speed of motor decoding[64]. Currently, there is significant variability in the signal processing strategies to decode motor information from the dorsal and dorsolateral spinal cord, ranging from low-frequency local field potentials[65] to higher-frequency signals[64], and more studies are required to characterize the source of these signals and how they evolve with time following SCI. It is hoped that adapting decoding strategies presently used in cortical motor decoding can advance the accuracy of spinal cord recording to a comparable level in the future.

From a clinical perspective, individuals with SCI often require spinal stabilization and decompression[66], presenting a surgical opportunity for the early implantation of spinal cord bioelectronic interfaces to aid in the rehabilitation of motor function after SCI. The proximity of spinal cord recording and stimulating devices also allow for a wired connection providing higher rates of information transfer, enabling the implantation of closed-loop spinal cord bioelectronic bypass interfaces to restore volitional motor function. We must be cognizant, however, that

implantation of spinal cord interfaces will necessitate surgical exposure beyond the site of potential decompression and stabilization with increased surgical risk and operating duration. Although there may be concerns that SCI induces proximal degeneration of the axons in a phenomenon termed dieback, studies have demonstrated that the dieback is limited to approximately 1-3mm from the proximal site of injury and that the process stabilizes after 4 weeks[67,68], allowing for most of the proximal spinal cord to remain a viable recording target.

## 2.2 Anatomy of the spinal cord

To efficiently target the spinal cord for electrophysiological recording, it is important to understand the underlying functional anatomy, details of which have been described in authoritative reviews[69,70]. In summary, the spinal cord comprises the outer white matter containing vertically oriented myelinated axons and an inner grey matter comprising of interneurons and modulatory fibres in a laminar pattern[71] transversely. The axons are grouped into ascending and descending tracts. The major descending tracts are the corticospinal tract, which is dominant in humans, the rubrospinal and reticulospinal tract[59], transmitting and modulating volitional motor signals via upper motoneurons from the cortex to the spinal cord. Lower motoneurons, receiving modulatory signals from intraspinal networks[72,73], then project axons to innervate muscle fibres, exiting the spinal cord via the ventral root. The major ascending tract comprises the dorsal column, transmitting proprioceptive and light touch sensation, and the spinothalamic tract transmitting pain and temperature sensation. The sensory fibres enter the spinal cord through the dorsal root, characterized by a fusiform enlargement housing the neuronal soma in the dorsal root ganglion. Finally, the spinal cord is covered by layers of pia, providing mechanical support to the surface of the spinal cord[74], and the arachnoid and dura, which together form a protective layer preventing the leakage of cerebrospinal fluid[75]. Spinal cord interfaces can potentially record from and stimulate the columns of the spinal cord or from the dorsal and ventral roots (Fig. 2). These columns are arranged in an ordered structure in the spinal cord, in contrast to peripheral nerves which contain bundles of both sensory and motor fibres without a specific order. Recording from the spinal cord thus has the advantage of adding spatial information, as signals obtained from an electrode with a known location can provide specific sensory or motor information based on which tract it is interfacing with. This is demonstrated practically in primate studies in which ventrally placed electrodes stimulated motor activity at lower thresholds than dorsal electrodes[76], possibly due to the proximity to descending motor tracts with ventral electrodes.

When applying functional anatomy to the design of spinal cord neural interfaces, we must be cognizant of the fact that the tracts are not arranged in a circumjacent pattern. Critically, there is significant radial overlap with the lateral column tract, with the descending corticospinal tract residing deeper than the ascending spinocerebellar tracts[77]. This implies that non-penetrating electrode arrays targeting motor information from the corticospinal tract will receive unwanted signals from the more superficially located tracts and penetrating electrodes have to be precisely placed to prevent mis-sampling. Further, the corticospinal tracts obey a somatotopic organization, with upper limb tracts located deeper than the lower limb tracts in the proximal cervical spinal cord[78]. This presents difficulties with the targeting of deeper white matter tracts with non-penetrating electrodes that may require advanced decoding algorithms to accurately localize the source of signals and exclude contributions from neighbouring axons.

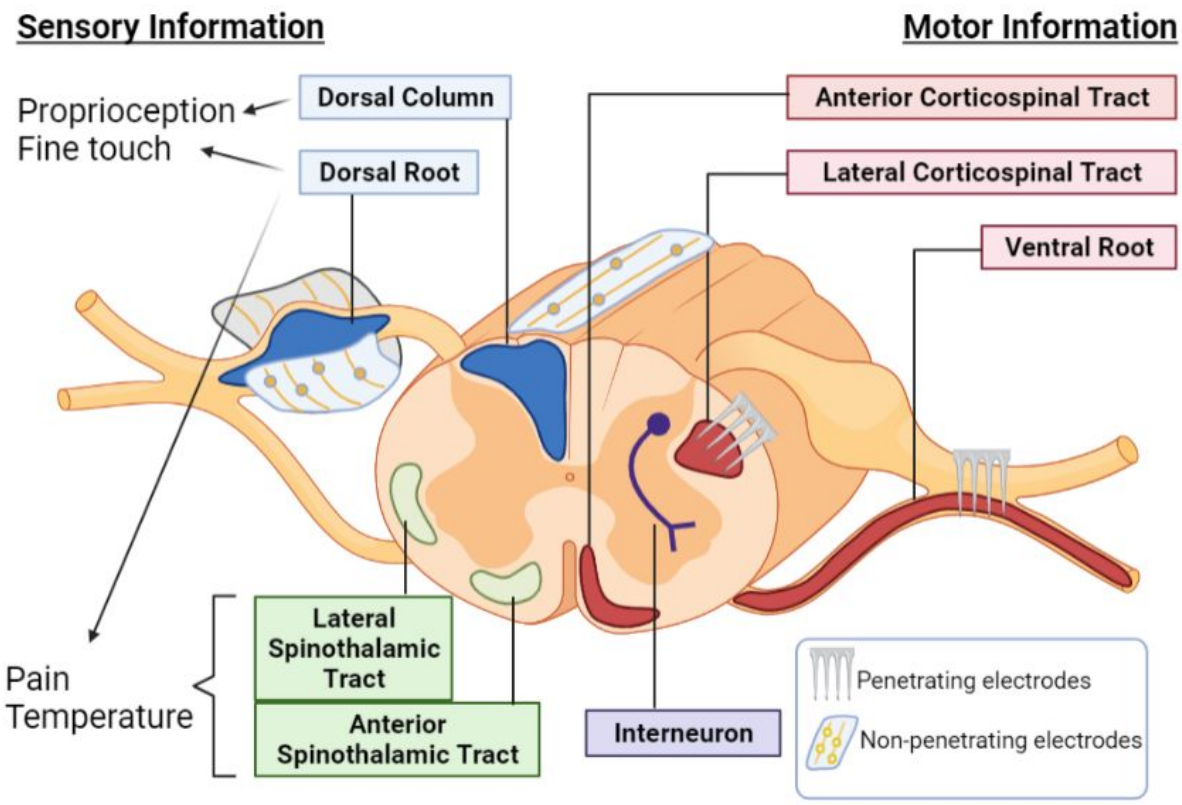


*Figure 2: Potential Spinal Cord Recording Targets: The spinal cord is arranged in ascending and descending tracts carrying predominantly sensory and motor information respectively. Targeting these tracts with both penetrating and non-penetrating electrodes could allow the recording and decoding of sensorimotor activity. Created with BioRender.com.*

## 3 Progress in Spinal Cord Recording Devices

### 3.1 Historical developments in spinal cord recording

Investigations in electrophysiology have been performed since the seventeenth century[79], but it was not until the 1930s did Gasser and Graham started extracting neural signals directly from the spinal cord using chloride-coated silver wires[80]. Eccles further explored the spinal circuitry, recording synaptic potentials with triggering of the reflex arc[81]. Frank and Fuortes were able to focus on the microcircuitry of the spinal cord using intracellular microelectrodes to discern specific neuronal structures[82]. Advances in experimental techniques enabled the next phase of spinal cord electrophysiology, allowing recording of spinal cord and dorsal root ganglion potentials in awake and behaving cats[83] and sheep[84]. Chronic recordings from the spinal cord, with the ability to extract multiple measurements across time and to correlate with animal behaviour, was established as a sophisticated electrophysiological method, although early electrode designs were beset by issues of breakage and inadvertent spinal cord injury[85].

### 3.2 Evolving role of spinal cord recording in electrophysiology

Before spinal cord recording was devised as a form of neural interface in spinal cord injury, it was initially developed as an electrophysiological technique, demonstrating the ability to study evoked local field potentials in the feline spinal cord[86] and defining the activity of interneurons in the spinal cord grey matter[87,88]. These studies were important as interneurons served a modulatory role in volitional motor control and reacting to sensory feedback loops. Further insight into how

interneurons modulate motor function was provided by Prut and Perlmutter, using intraparenchymal electrodes to investigate interneuron activity in non-human primates (NHP) performing wrist movement tasks[89,90]. Their findings described how interneurons function to regulate spinal premotor networks and suggest the role of this regulation in preventing undesirable motoneuron synchrony in states such as physiological tremor[91]. Additionally, Yanai et al[92] built upon the hypothesis that the cortico-motoneuron path undergoes further processing at the level of the spinal cord[93,94] by interneuronal networks[95], showing that interneurons transform cortical commands into muscle control signals that associate with specific coordinate frames. Interneurons also receive inputs from reticulospinal pathways to achieve their modulatory effect, as demonstrated by using electrodes implanted in the brainstem pyramidal and reticulospinal pathways to correlate with forelimb movements[96]. Further methods in chronic recording for electrophysiology were explored[85] and although early techniques led to complications of meningitis and spinal cord injury, it established the precedent for chronic recording of spinal cord signals. Recordings in awake, behaving subjects are important as they allow the correlation of spinal cord signals with motor volition instead of artificially evoked potentials.

Aside from investigating local spinal circuitry and firing characteristics, spinal cord recording enabled our understanding of the information flow from premotor cortex to activity at the level of alpha motoneurons[97]. Signals generated during volitional locomotion have also been investigated by Berg et al[98], using a customized frame to anchor extracellular recording arrays that could investigate lumbar spinal cord signal during rat treadmill locomotion. More recently, using modified spinal cord stimulators in individuals with postherpetic neuralgia, Wang et al were able to record spinal cord electrophysiological signals and correlate them with EEG signals[63], providing an opportunistic tool for studying corticospinal connections in humans. The use of spinal cord recording will continue to play a role in systems neuroscience, investigating the connectivity between cortical and peripheral signals.

### 3.3 Spinal cord recording: volitional motor signals

Advances in electrode and circuitry miniaturization paved the way for research into chronic spinal cord recording implants that can decode volitional motor activity. The group led by Mesut Sahin provided the foundation for spinal cord motor recording, first establishing the information capacity and transfer rate of spinal cord recording interfaces in cats[99,100] before demonstrating that elbow joint movements can be reconstructed with spinal cord recordings in freely behaving rats[101,102]. The electrode design was subsequently modified from non-penetrating to intraparenchymal electrode arrays, possibly to better target the deeper regions of the rubrospinal tract in rats[103]. This protocol allowed the correlation of spinal cord recordings with trained forelimb activity in a reach-to-grasp task via video-recorded coordinates of shoulder, elbow and paw positions[104]. Whilst Prasad and Sahin were able to demonstrate the long-term recordings of spinal cord signals, they were unable to record for more than 3 months, owing to the development of glial scarring and microwire breakage. In addition, it was reported that some of the animals sustained a SCI and could not be included in the study, emphasizing the risks associated with intraparenchymal electrode array implantations. To prolong the longevity of implanted electrodes, carbon fibre electrodes were also explored in the spinal cord in a pilot study[105], describing the SNR characteristics as well as possibly reduced microglial encapsulation.

Besides correlating spinal cord recordings with kinematic data, Sahin's group were able to reconstruct forelimb isometric forces[106] as well as electromyography signals[107] using computational

methods developed within their lab[64,108]. Although forelimb kinematic data had the greatest correlation coefficient, analyzing force and EMG data provides additional dimensionality to prediction models.

Increasing interest in BMIs in the management of SCI paralysis has led to more studies in the field of spinal cord motor recording. Spinal cord recordings were obtained from a common marmoset NHP model and correlated with upper limb kinematic data in a centre-out task[109]. The use of NHP models is advantageous when translating spinal cord motor recording to human trials as the corticospinal tract is more prominent in NHPs and humans compared to smaller animals. NHP models also allow for better validation of spinal cord interfaces in upper limb motor restoration due to their dexterity which cannot be replicated in smaller animal models. The use of larger animals also provides an anatomical dimension that is closer to that in humans which is especially valuable in juxta-clinical studies. Apart from investigating upper limb movements, Fathi and Erfanian decoded hindlimb kinematics in a treadmill ambulation task, comparing the predictive value of a dorsal column and lateral column recordings[65]. Studies investigating chronic spinal cord motor signal recordings are summarized in Table 1, including both electrophysiological and application-focused studies. However, we excluded studies that sacrificed the animal immediately after awake recordings, as the documentation of electrode survival and chronic complications was imperative to our analysis. It is interesting to note that although studies in spinal cord motor recordings have progressed both in the electrophysiological and engineering fields, there appears to be limited cross-pollination of ideas across both fields. This presents an opportunity for collaboration and integration, in which techniques used to harvest signals from the spinal cord for brain-machine interfaces can also be used to study corticospinal electrophysiology.

Besides interfacing directly with the spinal cord, the ventral root, carrying lower motor neuron axons to neuromuscular junctions, is also a potential target for recording and stimulating motor function. Though recordings from the ventral root have been obtained by Hoffer et al in locomoting cats[110], it was not until the recent decade that chronic, stable recordings could be obtained[111]. This could be due to the anatomical inaccessibility of the ventral root, residing deeper compared to the dorsal root ganglion. Whilst stimulation of the ventral root may play a role in SCI when placed distal to the level of SCI, recording from the ventral root is plausibly more useful in the setting of therapy in persons with amputated limbs, with neuroprosthetics that can be powered by motor volition[112].

Table 1: Chronic SCR in animal models (N/A: not applicable, N/R: not reported, CST: Corticospinal Tract, RST: Rubrospinal Tract, LCST: Lateral Corticospinal Tract)

| *Ref Year* | *Target site* | *Electrode design* | *Animal* | *Observed behaviour* | *Results* | *Complications* |
|---|---|---|---|---|---|---|
| *Ondrejčák et al[85] 2005* | C3/4, T11/12 dorsum | Epidural silver electrode | 11 Wistar rats (300-330g) | Open-field locomotion | Increasing stimulation voltage required over time to elicit evoked potential response in spinal cord | paralysis (1), broken electrode (2) |
| *Prasad et al[102] 2006* | C5/6 LCST, RST | Penetrating array with silicon electrodes and platinum tips | 4 Long-Evans rats (350-400g) | Face cleaning behaviour | CST and RST can both be used to reconstruct elbow angles | N/R |
| *Berg et al[98] 2009* | T11-L3 dorsum | Penetrating array with stainless steel wires | 6 Sprague-Dawley Rats (280-290g) | Treadmill locomotion | Demonstrated multi-unit recording of spinal cord signals during locomotion | Death (1), Failure of recording (1) |
| *Prasad et al[103] 2010* | C5/6 LCST, RST | Penetrating microelectrode array with platinum tips | 4 Long-Evans rats (350-400g) | Reaching or face cleaning behaviour | RST SCR correlated with timing of forelimb behaviour | N/R |
| *Prasad et al[104] 2012* | C5/6 LCST, RST | Penetrating microelectrode array with platinum tips | 4 Long-Evans rats (350-400g) | Reach and grasp task | Signal quality over time ranged from 50%-100% of original. Able to decode forelimb joint coordinates with SCR. | Wire breakage, connector failure, neural injury |
| *Kim et al[113] 2013* | L2/3 | Penetrating array with braided nichrome wires and polyimide insulation | Bullfrogs | N/A | Demonstrated ability of braided electrodes to obtain chronic SCR | N/R |
| *Guo et al[106] 2014* | C3/4 LCST/RST | Penetrating PDMS/polyimide array with gold contacts | 6 Long-Evans rats (350-400g) | Reach and lever press task | Correlation of SCR with forelimb forces (R^2: 0.58-0.77 in vertical direction) | N/R |
| *Debnath et al[111] 2014* | L6/7 ventral root | Penetrating floating array with platinum-iridium electrodes | 9 cats (3-6kg) | Treadmill walking | Demonstrated ability to record action potentials from the ventral root. Challenging insertion of electrode arrays | Broken leads (2), immune reaction (1), slow signal degradation (3), hardware/connector failure (1) |
| *Gok et al[114]* | C4 CST/RST | Flexible polyimide | 2 Long-Evans | Reach and | Prediction accuracy for EMG | N/R |

| | | | | | | |
|---|---|---|---|---|---|---|
| *2016* | | array with platinum contacts and PEDOT:TFB | rats | lever pull task | ranged from 0.5 in triceps to 0.88 in biceps | |
| *Cetinkaya et al[105] 2018* | C4 CST/RST | Penetrating carbon-fibre filaments | 2 Long-Evans rats (400g) | Face cleaning behaviour | Demonstrated suitability of carbon-fibre electrodes for chronic SCR | Microglial encapsulation (mild) |
| *Prins et al[109] 2020* | C4 CST/RST | Penetrating, floating array with platinum-iridium electrodes | 5 marmosets | nine-target reaching, two-target robot, touch screen tasks | Feasibility of chronic SCR in a small non-human primate model, ability to correlate with forelimb kinematics | Mechanical failure (3), Signal degradation (1) |
| *Fathi et al[65] 2021* | L3-4 DC and lateral column | Penetrating array with Teflon-insulated tungsten wires | 5 cats (3.1-4.2kg | Treadmill walking | Described spatial correlation of recording sites with hindlimb kinematics | N/R |

### 3.4 Spinal cord recording: sensory and pain signals

Motor signals represent only a facet of the sampling opportunities that spinal cord recording can provide. Sensory signals are also transmitted through the spinal cord dorsal column and spinothalamic tract, via the dorsal root and dorsal horn. Borisoff et al, using intraparenchymal electrodes in the dorsal horn of the spinal cord, correlated these signals with rat forepaw stimulation, demonstrating close to 100% accuracy in prediction of the time at which a sensory stimulus was presented[115].

Apart from interfacing with the dorsal spinal cord, the dorsal root ganglion represents a potential site for recording afferent sensory activity. Adapting flexible nerve cuff electrodes used in peripheral nerve recording, Sperry et al recorded activity in the DRG with the ability to perform simple source localization of the sensory stimuli[116]. This approach of using epineural electrodes was reproduced by Kashkoush et al who further demonstrated the recording of single-unit activity in the DRG[117]. Proprioceptive information can also be decoded from the DRG, enabling the decoding of joint position sense[118,119] and movement timing[120], possibly allowing for the design of neuroprosthetics with real-time sensory feedback[121].

The DRG also presents a valuable target in the study of nociception with the realization that intraspinal gate-control mechanisms modulate central pain perception[122]. DRG electrophysiology allows for the study of how different nociceptive peptides modulate DRG activity in a nerve section model[123] and chronic recordings by correlating with activity in the paraventricular hypothalamic nucleus[124] which is a source of neuropeptides. Protocols established by Urch et al allow for the recording of DRG signals with peripheral mechanical and electrical stimuli[125] whilst Zhao et al described the use of DRG recording in various neuropathic pain models[126].

Understanding of the role of local spinal cord circuitry in pain transmission has led to the clinical use of spinal cord stimulators (SCS) for neuropathic pain[127], with the mechanism postulated to be through local spinal cord gamma-aminobutyric acid (GABA) inhibitory mechanisms interacting with supraspinal mechanisms[128]. Using chronically implanted SCS devices in humans also enabled the recording of evoked compound action potentials, providing further insight into the type of sensory fibres recruited by SCS in pain modulation[129] as well as its longitudinal activation pathways[130]. This approach has also been applied in clinical use, using the evoked potentials generated by SCS to provide feedback in modulated doses that account for changes in impedance due to contact of the SCS devices with the spinal cord[131].

### 3.5 Spinal cord recording: bladder distension

Apart from the oft-studied loss of movement and sensation in SCI, bladder control issues afflict up to 80% of individuals with SCI[132], affecting not just self-esteem but also causing urologic complications such as infections and renal calculi. As the afferent signals from bladder filling also pass through the spinal tracts, the spinal cord and sacral roots represent a viable target for the detection of bladder filling. This has been demonstrated with intraoperative recordings of sacral root activity[133] and correlated with intravesical pressure measurements[134,135]. Recording these signals can be paired with sacral nerve stimulation to create closed-loop bladder emptying neuroprosthetics[136], improving on current open-loop designs such as the Finetech-Brindley stimulator[137] (Vocare® system, USA).

### 3.6 Role of spinal cord recording in neuromonitoring

Whilst spinal cord recording has progressed in experimental chronic animal implantations, it should be highlighted that the technology already has a widespread clinical role in the form of neuromonitoring. Neuromonitoring in the real-time evaluation of spinal cord functional connectivity via the observation of baseline activity and evoked potentials. These evoked potentials can follow either motor or sensory tracts[138] and be used to evaluated spinal cord function either indirectly or directly on the spinal cord via D (direct) waves. This allows the surgeon to reverse any step that may injure the spinal cord and is especially useful during deformity correction[22] and intradural surgery[20] with its ability to increase the safety margin of spine surgery established[23]. Spinal cord recording also serves to provide information on the level of injury in SCI and help to prognosticate the degree of motor recovery[139]. However, current modalities of direct spinal cord recording using D waves only capture information from the corticospinal tract fast-conducting fibres[140], leaving sectors of the spinal cord that could be monitored with more extensive mapping approaches[141] or more sophisticated time-frequency analysis of acquired signals[142]. In contrast to SCR applications in SCI, neuromonitoring focuses mainly on evoked potentials in a controlled, mostly static environment, which could explain why, despite its widespread clinical use, SCR paradigms in neuromonitoring have not driven advances in SCI neuroprosthetics.

## 4 Challenges in the clinical use of spinal cord bioelectronic interfaces

Whilst advances have been made in the use of chronic spinal cord recording devices in animal models, several obstacles must be overcome before these devices can be implanted in human trials. These challenges can be considered systematically from the device production line to surgical implantation and finally to precise processing of the acquired signals. We can thus compartmentalize the factors in several phases (Fig. 3): 1) Pre-implantation involving the consideration of electrode design and patient selection; 2) Peri-implantation where the clinician needs to respect anatomical boundaries during implant insertion and prevent acute complications; 3) Post-implantation in the chronic phase where biological reaction and the ability to consistently record signals become dominant issues. It is important to note the extensive interplay of factors: for example, the choice of electrode material can lead to repercussions across phases, such as how introducing stress-strain mismatch during implant insertion can also lead to eventual fatigue failure when used in the chronic phase. We further discuss the importance of preclinical studies investigating the safety and efficacy of potential SCR devices before translation into clinical studies. The ethical and regulatory issues surrounding the implantation of neuroprosthetics in the spinal cord will also be considered.

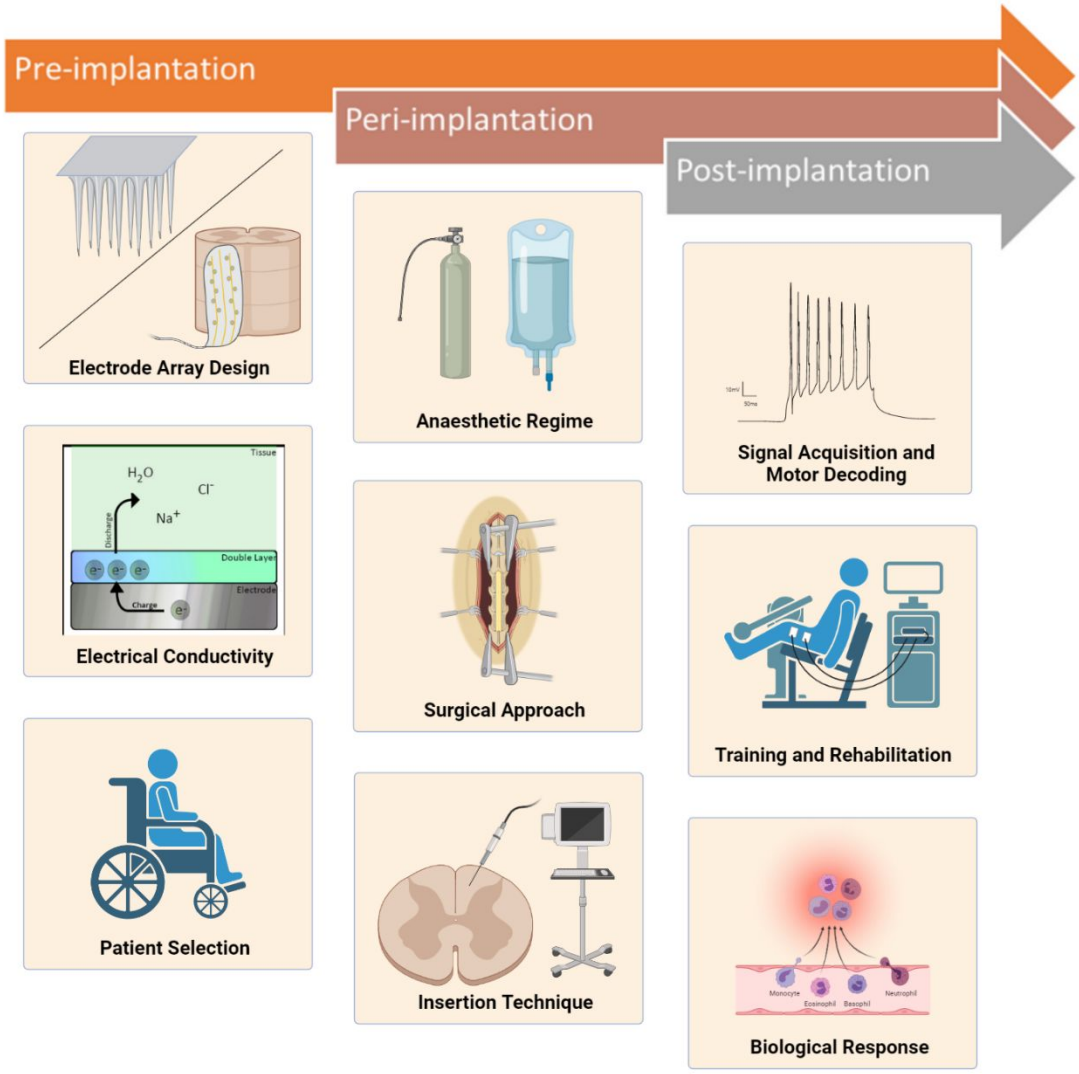


*Figure 3: Clinical challenges facing spinal cord recording devices at each phase of implementation, from pre-implantation to post-implantation. It is important to recognize that pre-implantation decisions, such as the choice electrode array material and design, can have downstream implications on the insertion technique, signal acquisition and decoding. Created with BioRender.com.*

### 4.1 Electrode conductivity

On a fundamental level, neural interfaces record electrical currents which have contributions from all excitable membranes, originating from various sources[143] from synaptic activity to voltage-dependent events and action potentials propagating along the axon as modelled by Hodgkin and Huxley[26]. Although recording electrodes can be placed intracellularly[81] and adjacent to neuronal membranes to isolate single-unit activity, these methods are less viable in chronic spinal cord recording due to micro-and macro-motion. The signals obtained in most studies are multi-unit and best described as compound action potentials (CAP), although lower frequency local field potentials (LFP) have also been correlated with movement kinematics[65] and bladder pressures[134]. The quality of

these recorded signals is paramount to the success of a spinal cord bioelectronic interface and in turn, this depends heavily on the electrical properties of the electrode. The ideal electrical properties are high conductivity, low impedance combined with material characteristics of flexibility and various materials have been used to achieve these goals.

The ideal impedance of an electrode depends on its function, whether it is a recording or stimulating electrode, the electrode array configuration, the amplifier characteristics, and the level of both noise and waveform distortion that is acceptable for a specific application. Generally accepted targets for recording electrodes measured at 1kHz lie in the ohm to kiloohm range, as they produce acceptable SNR levels[144,145]. However, polytrodes operating in the low megaohm range have been shown to have a negligible impact on SNR, providing an appropriate input impedance is used on the amplifier[146]. Within this range, it may also be important to consider impedance consistency across multiple electrodes as variability may lead to waveform modification and downstream signal processing problems. Impedance also affects the operation of stimulating electrodes. The two most important impedance associated measures of a stimulating electrode are how power efficient the system is and whether unacceptably high voltages will cause tissue or electrode damage[147]. Again, there is an acceptable impedance value range based on the specific application, primarily how much charge is being passed through each electrode but usually targeted in the ohm to kilohm range. Before designing a device engineers can use the Shannon criteria[147,148] to estimate the impedance needed for an electrode of a particular size to ensure that damaging effects are mitigated.

Metals were the first materials to be used as neural electrodes due to their excellent electrical conductivity although chronic implantation of some metals may lead to chemical dissolution and concerns of metal toxicity[149]. To avoid this problem and further improve the biocompatibility of the electrodes, semiconductors and conductive polymers (CP) have been developed. In particular, CPs such as 3,4-ethylenedioxythiophene (PEDOT) can be further doped to allow compensation of holes in PEDOT by poly(styrene sulfonate) (PSS) ions[150], creating a PEDOT: PSS material with greater electrical conductivity, allowing for superior signal-to-noise recordings[151] whilst maintaining the flexibility required in conforming electrode. On the other spectrum, carbon-based materials have also been developed as electrodes, possessing high tensile strength and stiffness, and have been trialled in spinal cord recording[105]. For a comprehensive technical review on electrode materials in neural interfaces, the reader is referred to the detailed analysis by Wellman et al[152].

Besides the choice of electrode material, the geometry of electrodes affects their electrical characteristics. Ideally, a spinal cord recording device will have decreased electrode contact area to increase the selectivity of the recording, however, this comes at the cost of increased impedance[153] and thus lower SNR. To overcome this, CPs can be deposited on the electrode surface to decrease impedance[154], at the same time increasing the biocompatibility of the electrode due to their corrosion resistance[155]. It is also ideal to have a large number of electrodes to increase topographical resolution[156] and classification accuracy. There, however, appears to be an optimal density of electrodes depending on decoding algorithms, as additional electrodes can increase computational burden and paradoxically decrease the classification accuracy by introducing noise[157] when observed in EEGs. Additionally, electrode density must be balanced with the consideration of electrode size, as having a high density may mean smaller contact areas leading to greater impedance and thus lower SNR[158]. Lastly, larger electrode arrays are associated with more extensive implantation risk especially with penetrating electrodes which can cause neural injury[159].

The design of the electrode array must critically consider its intended area of sampling (see **Anatomy of Spinal Cord**) as well as downstream repercussions with chronic implantation and long-term micromotion. Similar to cortical recording, electrodes in the spinal cord can be classified into

intraparenchymal and perineural devices (subdural and epidural), with non-invasive transcutaneous devices trialed[160,161] but demonstrating significantly lower SNR[162] due to noise from paraspinal EMG and the thick laminae protecting the spinal cord. Intraparenchymal arrays (Fig. 4) allow for targeting of deep structures in the spinal tracts such as inter-neuronal networks[163] and central pattern generators, spinal circuits responsible for producing autonomous rhythmic movements such as walking[164–167], although the significance of these circuits in the human are still a source of active discussion[168]. Implanting an intraparenchymal array, however, comes with attendant risks of neural injury even with the decreasing size of electrodes[159]. This may be mitigated with nanoscale[169] and flexible[170] devices but their insertion would invariably cause some degree of local trauma (see **Surgical Considerations**). Alternatively, non-penetrating electrodes (Fig. 5) can be used in the spinal cord, similar to ECoG arrays designed for cortical recording, to avoid issues with local tissue trauma. This strategy comes at the expense of limiting the areas of the spinal cord that can be sampled, although it is propitious that the white matter carrying the major tracts of the spinal cord resides peripherally and can be targeted via non-penetrating designs. This is facilitated by soft, pliant arrays that minimize the risk of chronic spinal cord deformation[171]. In using ultra-thin arrays, however, clinicians need to be cognizant of the practical considerations of intra-operative handling, as thin arrays tend to buckle during insertion[116] or may be susceptible to inadvertent damage such as tears. In this regard, redundancy in number of electrodes can be built into array design to prevent loss of critical sampling areas, similar to bipolar pacemakers with extra electrodes that can be used in case the primary electrode fails[172].

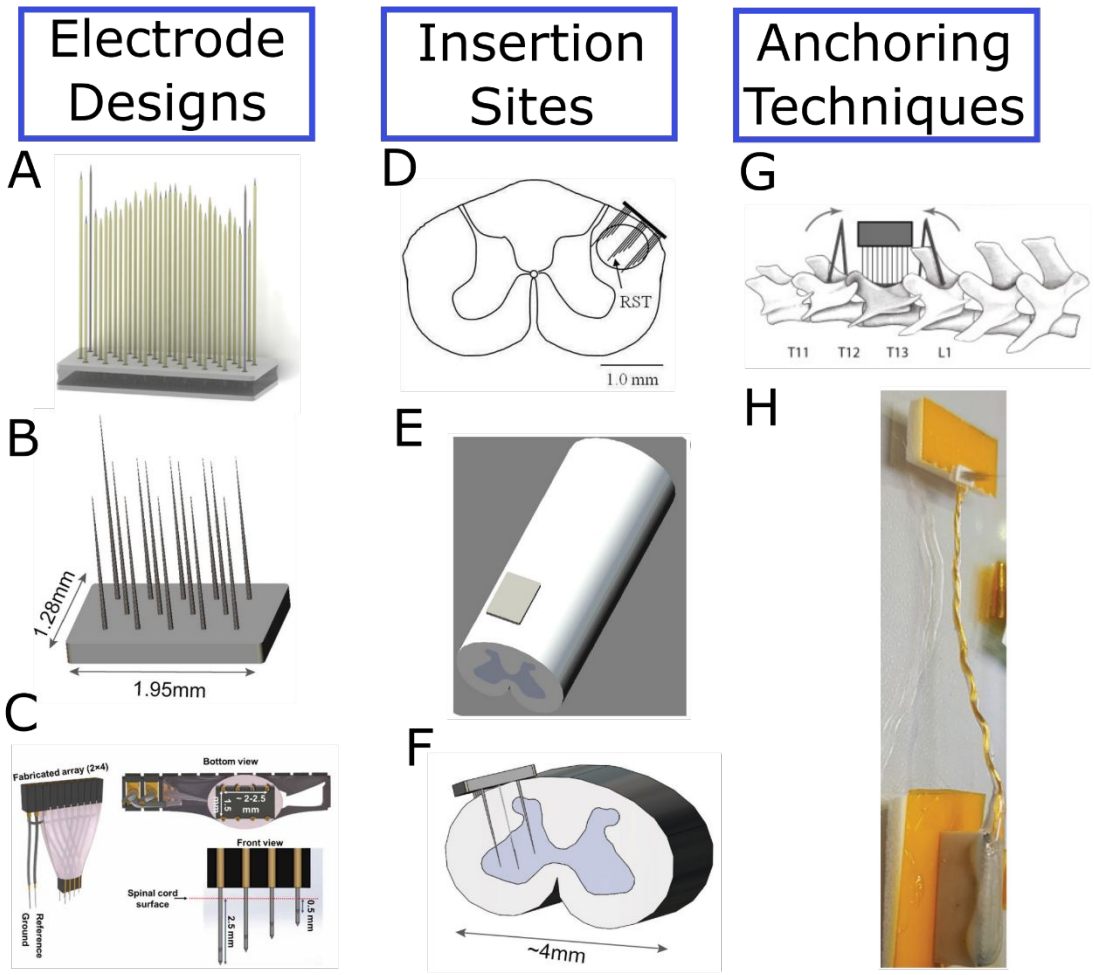


*Figure 4: Intraparenchymal SCR designs. The basic components of an intraparenchymal array consist of microelectrodes arranged in a uniform pattern[109,111] to increase the sampling coverage of a region in the spinal cord (A, B). Electrodes of varying depths can be used to provide additional dimensionality to the sampled area in the spinal cord, such as in the devices described by Fathi et al[65] (C). Microelectrode arrays have generally been used to target RST and lateral CST, both of which communicate motor signals[104,109] (D, E). To target areas of the spinal cord beyond the peripheral dorsal white matter, longer electrodes can be used to access the central grey matter, at the risk of greater penetrating trauma[109] (F). Previous techniques have used rigid anchors to hold the arrays in place, although this leads to neural injury and electrode breakage with chronic motion[98](G). This has led to the development of floating array designs, allowing the array to move with the spinal cord in motion while remaining connected to the digital components through flexible wires[109](H). Figure permissions: (A) reproduced from Debnath et al[111] under the terms of CC-BY licence. (B,E,F,H) reproduced from Prins et al[109]under an Institute of Physics (IOP) publishing licence. (C) reproduced from Fathi et al[65] under an Institute of Physics (IOP) publishing licence. (G) reproduced from Berg et al[98]under Science, Technical and Medical (STM) permissions guidelines.*

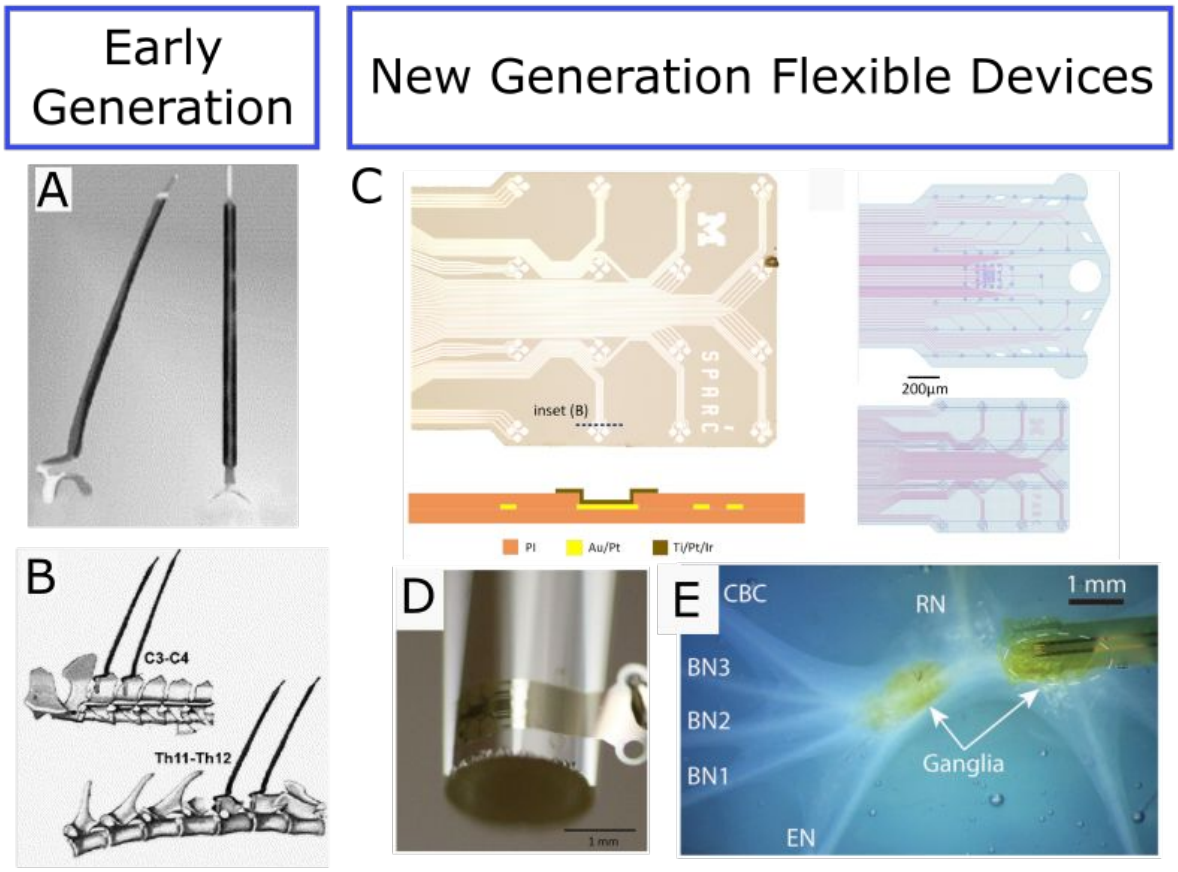


*Figure 5: Epineural SCR designs. Early designs used rigid materials to achieve spinal cord recordings but this led to chronic neural injury as well as electrode fracture as described in the electrophysiological experiments using silver epidural electrodes by Ondrejčák et al [85](A, B). To mitigate the stiffness mismatch, lessons gathered from peripheral nerve and brain interfaces has inspired the designs of flexible electrodes. Sperry et al designed a flexible polyimide (PI)-based electrode array (C) that can curve over the surface of a 2mm diameter rod (D) and conform to neural structures such as the dorsal root ganglia to reduce the risk of chronic neural injury[116](E). Figure permissions: (A, B) reproduced from Ondrejčák et al[85]under Science, Technical and Medical (STM) permissions guidelines. (C-E) reproduced from Sperry et al[116] under an Institute of Physics (IOP) publishing licence.*

A key component of an ideal electrode is the insulating layer, blocking unwanted electrical conduction whilst retaining good adhesion to the underlying electrode. Common insulating elements include polyimide[173], parylene[174,175], and silicone derivatives[176] with newer insulators possessing lower stiffness and better biocompatibility. The fabrication process is especially vital as arrays obtain higher electrode density, as even small defects in insulation can lead to electrical cross-talk[177]. Adhesion of the insulator is especially important in the manufacture of planar arrays via microlithography, as imperfections may allow ingress of cerebrospinal fluid, leading to delamination of insulator from the electrode[178].

A full-fledged neuroprosthetic used in SCI is not complete without digital subcomponents such as analogue-to-digital converters and power sources, all of which are subjected to the same biological and mechanical stresses as the electrode interface. Packaging of these components must be meticulous to prevent fluid ingress[179] and flexural junctions should be protected to prevent fatigue failure. Another consideration is how the electrode array is anchored to the surrounding bony

structures. We envision that a rigid anchor will not be able to tolerate the movement of the spinal cord during physiological movement[180] and thus a floating array may be more suitable[109], although this translates to motion along the flexible interconnectors which must be balanced. Wireless spinal cord interfaces could reduce device failure at connecting junctions[181], although issues in information transfer rate and power supply have to be resolved before clinical deployment.

### 4.2 Material considerations

In long-term implantations, the mechanical characteristics of the electrode get increasingly significant in allowing continued recording and preventing neural injury. The Young's modulus (*E*) of the spinal cord is several orders lower than current flexible electrodes[182], with neural tissues exhibiting a Young's Modulus in the kPa range, common polymer substrates in the range of 0.5 MPa to >1GPa, and ubiquitous conducting metal electrodes exhibiting a Young's Modulus of 10s to 100s of GPa[183]. These differences will thus lead to stiffness mismatches between biological tissue and electrical interfaces which has been shown to drive biological tissue responses[184] with glial reaction, eventually leading to diminished recording capabilities. To compound this difficulty, the spinal cord is an anisotropic structure with the grey matter two times stiffer than white matter[185], which means that electrodes optimally designed for grey matter recording may prove too stiff for the white matter.

In chronic implantations, fatigue failure of the electrodes must also be considered[186], although advances in flexible materials can address this obstacle adequately[187]. Dissolvable materials and carrier vessels may help to reconcile the need for adequate stiffness during insertion yet prevent chronic mechanical mismatch[188]. Additionally, advances in materials such as hydrogels, cross-linked polymers that bear mechanical similarities with biological tissue[189,190], can potentially decrease modulus mismatch complications yet possess the ability to conduct ionically and function in bioelectronic recording/stimulating[191].

Spinal cord bioelectronic interfaces have adopted advances in both brain-machine interfaces and peripheral nerve interfaces[192]. Whilst it is tempting to consider the mechanical environment of the spinal cord to be on a spectrum between the stable brain and mobile peripheral nerve, some characteristics are specific to the spinal cord. The spinal cord resides in a dynamic environment with movement within the subarachnoid space attributed to vascular pulsations[42], eccentric positioning[43] and physiological flexion[180]. In addition, unlike peripheral nerves which can be mobilized safely and are resistant to a minor injury, the spinal cord is particularly sensitive to trauma. Thus, strategies such as Flat Interface Nerve Electrode[193] cannot be safely considered in the spinal cord as it relies on compressing the nerve to gain proximity and maximize spatial resolution, whilst the adoption of nerve cuff designs must be approached with caution to prevent chronic spinal cord constriction. When designing devices that can last the lifetime of the patient, we must also be cognizant of the changes in spinal cord dimensions with age[194] that can affect the precise location of electrodes, although emerging stretchable neural interfaces may help adapt to these changes[195].

### 4.3 Patient selection

As exploratory bioelectronic devices in SCI transit to early human trials[196,197], we anticipate that neuroprosthetics will gain widespread acceptance as a standard in SCI management in the near future. Once the technology and accompanying evidence start to mature, it will become imperative

for clinicians to select the right individuals for this treatment to maximize clinical outcomes. The factors to consider can be divided into disease, patient and institutional factors.

## Disease factors

SCI is a heterogenous condition, with varying levels and completeness of injury according to the 5 grade American Spinal Injury Association (ASIA) Impairment Scale[198] (AIS), with AIS A indicating a complete SCI with no sensory or motor function below the level of injury and AIS E referring to intact neurological function. Individuals with AIS C-E SCI have a good prognosis, with 70-90% predicted to regain ambulatory capacity[199,200] and the risk of implantable neuroprosthetics may not outweigh the benefits, although this group have demonstrated good response to spinal cord interfaces in rehabilitation[9]. The cost-benefit ratio of neuroprosthetics is much more significant in individuals with AIS A/B SCI, as their grade of injury is unlikely to improve especially after 3 months[201] and less than 10% are expected to walk at 1 year[202].

The level of injury is another major predictor of SCI functional outcomes as it dictates the motor units preserved, with mid-thoracic injured individuals depending on wheelchair and 5$^{th}$ cervical segment injured patients losing independence in activities of daily living[203]. More importantly, individuals with upper cervical injuries lose the function of respiratory muscles and depend on long-term ventilators[204]. This presents issues with motor rehabilitation capacity and the priority for these individuals may instead be neuroprosthetics that can electronically pace the diaphragm, weaning them off ventilators[205]. Additionally, SCR may not have a viable surgical target in high cervical injury and motor volition may need to be extracted from the cortex.

The duration following SCI and neuroprosthetic intervention is also key in choosing individuals who have the best chance of improvement. Given that a small proportion of individuals do improve from an AIS A/B injury[201], it is reasonable for clinicians to observe the plateauing of functional progress before offering neuroprosthetic implantation surgery[206]. With better acceptability and clinical evidence of neuroprosthetic success in the future, however, individuals with AIS A/B injury may be willing to undergo spinal cord neural interface implantation at the time of surgery to reduce the risk of secondary spine surgery. Muscle atrophy sets in rapidly after SCI, with individuals losing 18-46% of muscle cross-sectional area 6 weeks after injury[207]. This is of great concern to clinicians, as the success of potential spinal cord bioelectronic bypass devices depends on functioning motor units to restore motor function. Fortunately, long-term studies have found that muscle atrophy stabilizes in individuals with SCI at 14-20 years of follow-up[208]. Further, with recognition of the role of rehabilitation in spinal cord injury[209] in preserving muscle volume[210], coupled with the use of exoskeletons to preserve ambulatory motor memory[211], we believe that duration after SCI should not be a strict contraindication to neuroprosthetic implantation and that an individual assessment of potential motor recovery will be more appropriate. Likewise, the age of the patient should not preclude potential recipients of neuroprosthetics, as older individuals can improve similarly with rehabilitation, albeit at a slower pace[199]. Additionally, individuals with SCI develop debilitating joint contractures[212] that will compromise movement recovery, necessitating regular physiotherapy sessions for passive range-of-motion exercises and appropriate anti-spasmodic injections[213].

## Patient factors

The selection of an ideal candidate will be essential to the initial success of neuroprosthetics in SCI, and it is usually with the maturation of the clinical use of a novel medical device that the selection criteria can be expanded. The recent human pilot trials[9–11] describe an intense rehabilitation schedule, with participants committing up to 5 days a week over 43 weeks to achieve the desired response. Adherence to such a regime requires highly motivated individuals who can persevere despite the near 50% incidence of mental health issues following SCI[214,215], likely with the help of facilitative socioeconomic conditions[214]. Besides the psychological demands, clinicians need to assess the physical fitness of candidates, as SCI is associated with increased cardiovascular[216] and respiratory[217] complications that can worsen with overexertion.

Institutional factors

The management of a SCI patient requires a multidisciplinary effort[218] and this will be compounded with the mainstream use of neuroprosthetics. The acute implantation will require a surgeon who understands the downstream effects of implantation trauma and poor sampling, working in concert with a neuromonitoring team who can communicate accurate placement of devices intraoperatively. Post-operatively, the patient will need to work with rehabilitation therapists as well as signal processing scientists to decode the patient's intended movements. Lastly, the team needs to work in an environment equipped with real-time electrophysiological monitoring, gravity-assist devices for effective rehabilitation and a video-capture set-up for monitoring progress. Implanted neuroprosthetics is capital and labour-intensive endeavour, though healthcare policymakers need to understand that even preliminary reports on neuroprosthetics demonstrate good health care value[219,220].

### 4.4 Surgical Considerations

Even before accessing the spine, implanting neuroprosthetics require individuals to be under general anaesthesia to allow for safe surgical exposure. However, anaesthetic agents perturb neurological activity[221] and the choice of an optimal agent and dose is vital especially if position of the electrodes is confirmed via intraoperative electrophysiology. Whilst urethane is commonly used in small animal electrophysiological studies, its use is precluded in humans due to its carcinogenicity[222]. It is likely that an experimental procedure involving neuroprosthetic implantation will follow current guidelines in neuromonitoring for neurological surgery and that Total Intravenous Anaesthesia may be preferred due to the ability to rapidly titrate the depth of anaesthesia when intra-operative electrophysiological implant placement checks are required[223].

The spinal cord is a deep structure, protected by layers of skin, subcutaneous tissue, paraspinal muscle and bony laminae. Spine surgeons are adequately trained to avoid risks of spinal cord injury, haemorrhage during exposure, but haemostasis must be even more meticulous as blood can adversely affect the quality of implant performance. Depending on the intended design of the electrode array, the dura may require incisional exposure, and it is worth noting that the human cerebrospinal fluid under the dura occupies a greater relative volume than small animals and may perturb signal recording due to their conductive effects[39]. Also, implants that breach the blood-brain barrier may lead to local ischemia and infiltration of neurotoxicity and pro-inflammatory factors that degrade electrode performance[224].

The next challenge is accurate placement of intraparenchymal electrodes whilst avoiding the rich peri-spinal capillary network[225], a delicate procedure that would certainly be performed under microsurgical guidance, although emerging approaches by Neuralink are exploring the use of robotics and advanced imaging to better identify and avoid blood vessels for accurate and safe electrode placement[226]. To prevent local vertebral motion accelerating electrode failure, adjacent vertebrae can be surgically fused. The surgeon would also need to decide on a means of anchoring the device and protecting these electronic devices with specialized housing.

Strict antiseptic protocols must be adhered to, as any infection of such an experimental neuroprosthetic device would be devastating[227]. Risks associated with surgical exposure may be mitigated with minimally invasive techniques developed for existing spinal cord stimulators[228,229], especially when coupled with minimally-invasive expandable neuroprosthetics to allow greater coverage of recordings through smaller incisions[230]. Nevertheless, surgeons implanting these novel devices must consider the technical aspects of implant removal which may be needed for infection, device failure or for reasons such as Magnetic Resonance Imaging incompatibility[231]. The basic principles of revision spine surgery can be applied, understanding that scar formation can distort normal anatomy and that this process occurs at the electrode-tissue interface and that improper removal techniques can cause harm to underlying neural tissues. In this respect, non-penetrating devices may be more easily explanted without causing damage to underlying tissues.

### 4.5 Signal Acquisition and Processing

Whilst recording of evoked potentials in an acute, non-recovery animal model is well-established[232,233], the challenge of securing stable, chronic recordings in a behaving animal or human is increased exponentially and is a function of many variables, some of which are beyond the clinicians' control. Even before acquiring the signal, the selection of spinal cord level at which to record signals is imperative to the success of stable chronic recording. Whilst the dieback of axons in SCI is limited to millimetres[67], the clinician must be cognizant of other pathological processes that may impede the survival of proximal axons. SCI in humans is characterized by cystic degeneration[234], similar to that observed in rat models[235]. In some individuals with SCI, this degeneration follows an ascending course, leading to further functional impairment[236]. To complicate the clinical assessment, syringomyelia, in which a fluid cleft forms in the spinal cord, is associated with SCI and may lead to rapidly deteriorating sensory and motor function that, in certain cases, require surgical alleviation. Ideally, recording just above the site of SCI would provide the greatest volume of neural information, but these complex post-traumatic complications affect the suitability of recording adjacent sites in SCI. Fortunately, the advances in imaging have provided a high fidelity means to assess these complications[237] and it will be important that any SCI patient receiving a recording implant undergoes pre-operative imaging to acutely define the extent of SCI and surrounding areas of injury. Imaging can be further enhanced with intraoperative localization techniques[238,239] to confirm that the right level of device implantation is performed.

The principles of neural signal processing[240] can be applied to spinal cord recording, although there are unique challenges accompanying each phase of processing (Fig. 6). In the signal acquisition and recovery phase, recording from the spinal cord has the advantage of being insulated from paraspinal muscle EMG artefacts due to the surrounding bony structures. However, other biological sources of artefacts such as echocardiograms (ECG) and vessel pulsations are likely to persist[241]. More prominently, the displacement of the spinal cord during physiological flexion[180] is likely to generate movement artefacts which must be accounted for when filtering the signals. To better minimize

these sources of noise, neural devices require a stable interface with the spinal cord which may require anchoring to the dura. The housing for the electrical assembly should also serve to minimize external sources of noise as even the leads and cables are susceptible to external noise[242]. Bandpass filtering has been used in most of the chronic animal studies with the lower band filtering ECG, power supply noise whilst the upper band can address spikes from unintended changes in contact of the bioelectronic interface, especially with non-penetrating electrodes. When interpreting motor signals, however, caution must be applied in filtering signals as the process alters the temporal accuracy of the signals[243], leading to movement that does not respond to volition in an appropriately-timed manner.

As described (see **Anatomy of Spinal Cord**), the overlap between ascending and descending tracts in the lateral column can pose a significant challenge when recording motor signals. This issue was highlighted by Prasad et al[101], severing the overlying spinocerebellar tract to eliminate sensory activity in the recordings. Despite this, the presence of multiple peaks and observing the directionality of electrode activation indicated that ascending fibres were still activated, reducing the accuracy of motor decoding. This was subsequently addressed by the authors by choosing a reference electrode away from the spinocerebellar tract[103]. With improved multimodal spike-sorting algorithms[244], morphological characteristics of motor signals could potentially be extracted and isolated to reduce sensory contamination.

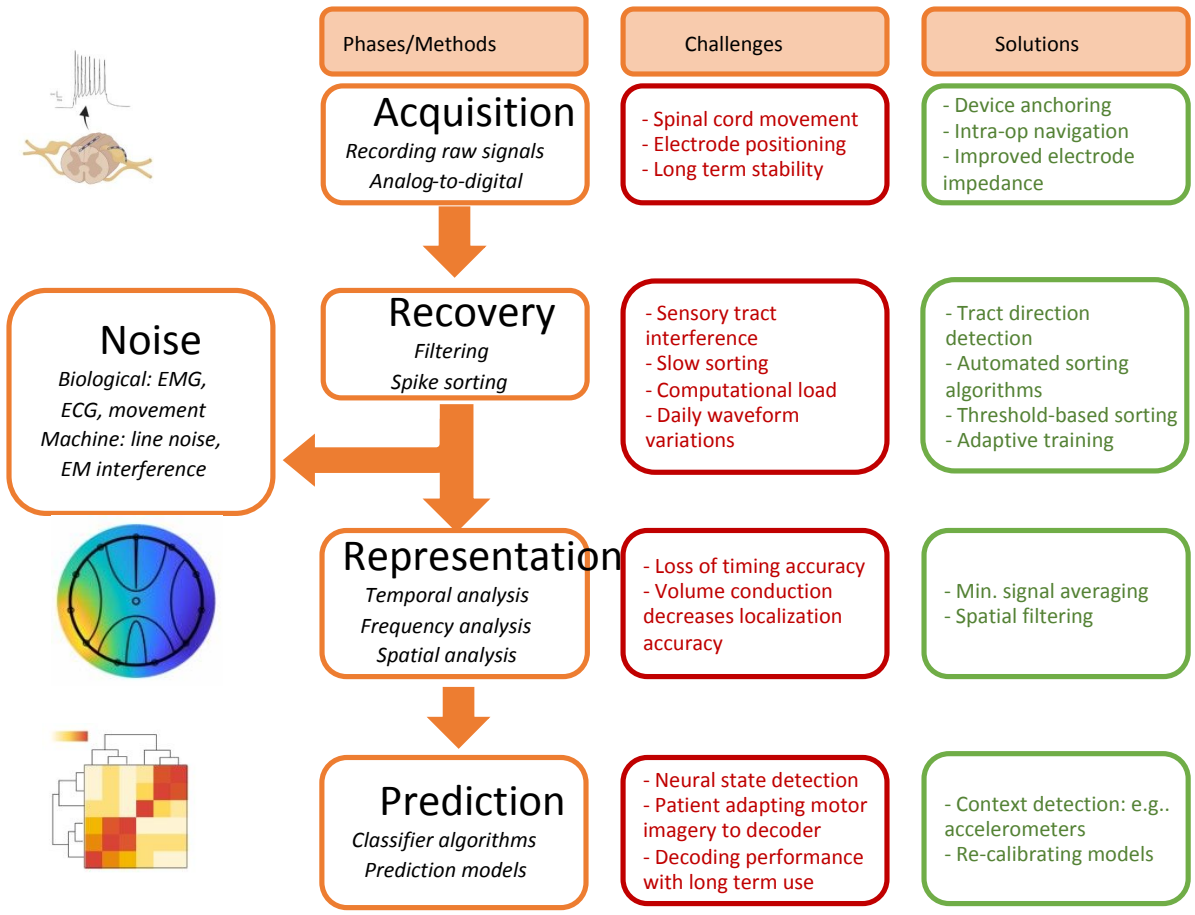


*Figure 6: Basic phases in spinal cord neural processing, challenges and possible solutions. Challenges can be encountered with each phase of signal acquisition and decoding. Importantly, stability of decoding performance with long term use of spinal cord recordings has not been demonstrated yet.*

The next challenge is the accurate representation and decoding of spinal cord signals. Spike sorting can be performed to extract signals of interest, with automated spike sorting algorithms being especially accurate[245,246] in cortical recordings. However, spike sorting may be computationally intensive and threshold detection may be a more efficient method of identifying signals of interest[247]. The computational intensity will be more relevant as the number of recording channels increases. To discern the motor signals of interest from noise generated by sensory signals, spatiotemporal patterns can be studied since the sensory and motor fibres have varying conduction velocities and spatial representation in the spinal cord, extending concepts from similar decoding in peripheral nerves[248]. More importantly, to function well over the course of a patient's daily activities, the device must decode the signals in the context of activity, whether the patient is at rest or performing a task[249]. This is especially practical during sleep states, where dreamed activity have been demonstrated to elicit sensorimotor cortex signals[250], although whether this activity is transmitted downstream to the spinal cord or inactivated in the midbrain is still not established. Integrating accelerometer data with recorded signals has been suggested as an adjunct to differentiating between resting and active states[251].

It is important to note that signal processing in clinical use devices will not be a static process and that it is difficult to track the activity of a specific population of neurons chronically as evident in studies on cortical motor neurons[252]. This problem may be compounded by the increased movement

in the spinal cord and inconsistencies in electrode contact. User feedback may help to alleviate this issue with re-calibration of the decoder during each training session if operated in a closed-loop fashion. However, when training is applied in an open-loop manner, it has been suggested that the user may respond in anticipation to what he thinks the decoder requires, leading to changes in the acquired neural features[34,253]. A re-calibrating training model proposed by Gilja et al[62] incorporates the user's intention to complete task goals with adaptive decoding to improve prediction, leading to stable signal representation over time.

Signals recorded from the spinal cord must be able to predict the users' intended movement and generate corresponding control signals for the stimulating devices. Spinal cord recordings have been demonstrated to predict for limb position[104], motor force[106] and EMG[107] with correlational coefficients ranging from above 0.7 for limb prediction to 0.67 for limb forces. Whilst this degree of correlation is commendable for animal trials, we envision that use in humans requires a much higher prediction accuracy, possibly with the training of robust machine learning algorithms[254]. Relating to implementing closed-loop spinal cord bioelectronic bypass, the information transfer rate of control signals is also an area of academic debate, with rates of 6.5 bits/second achieved by current neurotechnology[255], although Lebedev et al argue that information transfer rate should not be the ultimate matrix in assessing the success of neural interfaces[256]. It is also important that the decoding performance remains stable over the long term which has been demonstrated in cortical-based interfaces[257] but has yet to be shown in spinal cord recording devices.

Wireless devices increase patient acceptability[5] and are likely to be the model for human implantation. Fortunately, improvements in power capacity have enabled the use of wireless neural recording devices[258,259], without compromising the bandwidth of transmitted data[260]. Even with advances in wireless charging technology, however, deterioration in battery capacity in the long term must be anticipated. This is seen in clinical-use deep brain stimulator devices[261] and the future need for surgical procedures to change the battery of spinal cord bioelectronic bypass devices must be explained to prospective individuals.

### 4.6 Biological considerations

Beyond acute biological reactions of metal hypersensitivity[262] and infections, the clinician implanting neural interfaces must be aware of long-term implant-related complications that can compromise chronic recording, through a comprehensive understanding of the underlying cellular processes that occur after a foreign body is introduced into neural tissue. The sequence of these biological processes is similar to the body's wound healing response[263,264], although there are differences specific to the cellular response of neural tissue injury[265,266], termed foreign body reaction (FBR). The acute response is initially characterized by cellular injury and haemorrhage from disruption of the blood-brain barrier, mediated by astrocytes and microglia interacting with cytokines as well as a coagulation response activated by platelets and plasma proteins. The extent of this phase is a function of insertion trauma as well as electrode tip morphology and dimension[159], with slow insertion shown to improve quality of recordings[267] due to increased neuronal survival along the insertion track. The use of image guidance to avoid blood vessels can also limit the haemorrhagic response[268], whilst incorporating surgical robots could enhance the precision of implantation and reduce the creation of false tracts[226].

Following the acute trauma, increased capillary permeability and chemotactic factor release permit the recruitment of neutrophils able to release degradative enzymes to remove debris. This results in

a challenging environment for biocompatibility, as pH can be as low as 4[269]. The impact of the acute inflammatory phase can be potentially reduced with the use of non-penetrating electrodes[270], although the foreign body reaction still exists and could lead to a layer of fibrosis underlying the array[271].

The acute phase transits over a week into a chronic inflammatory phase with alterations in cellular milieu, with astrocyte and reactive glial activity increasing, depositing extracellular matrix around the implant. The course of the acute phase can be dependent on the stability of the electrode as well as its stiffness[272], especially since micromotion is unavoidable in any chronic application and stiff electrodes will incite a greater degree of ongoing neural injury compared to soft materials. The glial response extends beyond encapsulation, as more recent research has demonstrated that it can influence protein phosphorylation and lead to local neurodegeneration[273], further deteriorating the long-term recording capability of electrodes. The impact of glial scarring and signal recording impedance is a complex interaction between cellular and mechanical processes and still not yet completely understood[274]. It is known that a mismatch in stiffness of electrodes and neural tissue is a driver of persistent foreign body reaction, which can be minimized with the use of flexible electrodes[187,275]. To balance the technical difficulty of inserting a soft flexible electrode with consideration of long term stiffness mismatch, dissolvable insertion shuttles have been proposed, allowing precise control during insertion yet avoiding long-term issues of stiff electrodes[276]. Of greater concern, the FBR can be exuberant in rare cases, leading to mass compression of the spinal cord which has been reported in stimulators implanted for pain control[277]. The eventual formation of fibrotic tissue as a consequence of FBR also leads to degradation of recorded signals due to increased impedance[278] and loss of selectivity in both stimulation and recording. The fibrotic tissue can however be useful in spinal cord intraparenchymal electrodes, where it can serve to anchor the position of the devices[279].

Strategies to minimize the biological foreign body reaction can target the cellular mediators of inflammation and fibrosis. Whilst factors such as electrode coating with hydrogels[280] and roughness can influence the degree of inflammatory response, the use of smooth microgel coatings on its own is not sufficient to modulate foreign body reaction[281] and anti-inflammatory agents may be required. Dexamethasone, a synthetic steroid with anti-inflammatory properties, has been used in the coating of electrodes[282,283] and flexible substrates[284], reducing the thickness of glial encapsulation[285]. Besides dexamethasone, non-steroidal anti-inflammatory agents such as aspirin have also been shown to decrease foreign body reaction[286], although the use of these agents must be balanced with the increased risk of bleeding especially in the early post-traumatic period following SCI[287]. Following the success of cytokine modulators in human autoimmune disease, Interleukin-1 receptor antagonists have been used with conductive polymer coatings to create sustained-release anti-inflammatory properties[288], showing reduced cell adhesion, although it remains to be seen whether this translates to improvements in chronic neural recording.

Foreign body response can also be modulated downstream of the inflammatory cascade by using anti-fibrotic agents. Transforming Growth Factor-beta and its downstream pathways feature in fibroblastic activation and present a target for modulation[289]. Recently, colony-stimulating factor-1, implicated in the differentiation of macrophages, has been identified as a target for inhibition and limiting the fibrotic response[290]. We must be cognizant, however, that the fibrotic response differs in cortical and spinal cord neural tissue versus other tissues in terms of cellular response[291] as well as the extracellular matrix, most notably with the absence of collagen deposition[292]. Addressing the fibrosis alone without understanding the adjacent neurodegeneration caused by the fibrotic process[273] will not resolve the chronic deterioration in spinal cord signal acquisition.

By incorporating cell transplantation on to electrode interfaces, biohybrid implants[293] can serve as a bridge between the host neural tissue and the foreign electrode interface. These biohybrid implants can minimize FBR through a stable cell-electrode interface that prevents degradation by the host immune response, leading to increased peri-implant neuronal survival for better chronic recording[294]. In addition, the double interface between cell-electrode and host tissue-cell promotes better integration of the electrode with cells that are directed by chemotactic factors to grow into the surrounding host tissue, thereby also reducing acute modulus mismatches between host tissue and electrode. Biohybrid devices can be created via direct seeding of neural stem cells onto the electrode surface[295], although early studies demonstrated more than 90% cell viability loss post-implantation. Alternatively, cultured neurons can be carried within degradable hydrogels and conductive polymers[296], with the degradation of the hydrogel reducing stiffness with time yet allowing high initial neuron survival rates. This technology, though promising, is still in its infancy and challenges regarding cell adhesion, survival and autoimmune reaction will have to be overcome before clinical use.

### 4.7 Translating from preclinical to clinical studies

Acquiring knowledge from the anticipated challenges in clinical SCR will aid the design of robust preclinical studies. Whilst pioneering work by Prasad[104], Fathi[65] and colleagues have provided initial data on the viability of SCR in decoding limb kinematics, more preclinical work needs to be done to evaluate the safety and efficacy of potential SCR-based neuroprosthetics before pilot clinical trials. Fortunately, the development of these devices can parallel the preclinical investigation phases used by previous neural interfaces summarized in a review by Shepherd et al[297], and it is important to note that ongoing feedback from preliminary results is vital to allow the continual advancement of device prototypes.

Regardless of the choice of device material, in vitro safety and reliability has to be demonstrated. The electrodes used should undergo tensile tests to demonstrate is stability in a dynamic environment and impedance characterization to document long term electrical stability[298]. Evaluation of devices using accelerated ageing protocols are also useful to extrapolate the long-term degradation of devices[299]. The development of quality standards for SCR devices can be aided by definitions provided in International Organization for Standardization (ISO) documents such as ISO 10993-1[300] “Biological evaluation of medical devices”.

In vivo studies are essential in preclinical testing of neural interfaces and the selection of an appropriate animal model is important. Previous animal models used have included rats[104], cats[65] and non-human primates[109], and whilst these animal models have been established as models for SCI[301], specific anatomical differences such as in the location of spinal cord tracts have to be accounted for in preclinical testing[302]. The safety and efficacy of SCR devices can be broadly evaluated in acute and chronic settings, and several key features must be demonstrated. Firstly, the spinal cord is susceptible to iatrogenic injury, and neuromonitoring during insertion of experimental SCR devices in animals may help detect and mitigate this risk[303]. Secondly, SCR devices must demonstrate the ability to record neural signals in the acute setting, which can be validated by intraoperative stimulation of the motor cortex[304]. The more pressing challenge, however, is the demonstration that reliable recordings can be achieved in the chronic setting, ideally throughout the lifespan of a patient with SCI. Whilst Prasad et al demonstrated that SCR signals can be used to decode forelimb movement up to 3 months post implantation[104], the initial data suggests that signal amplitude begins to deteriorate at 4 weeks post implantation and is attributed by the authors to the

formation of reactive scar tissue around the electrodes. Additionally, the quality and stability of SCR signals is further complicated by possible reorganization of local spinal motor circuits above the level of injury[53] and the long term stability of SCR signals has yet to be demonstrated by in vivo models, for durations longer than 3 months. Last but not least, the biological safety of implanted SCR device must be demonstrated with both behavioural data describing locomotor deficits and immunohistochemistry to characterize the degree of glial reaction and astrocyte activation in and around the spinal cord[277].

Concurrently, SCR device prototypes can be developed for clinical use through human cadaveric studies. These studies are critical to adapt implants to specific human spinal cord dimensions[302], review the surgical techniques as well as anticipate possible anatomical obstacles to device implantation. Prior to clinical testing, cadaveric studies are also essential for surgeons to revise the operative procedures, especially for such experimental devices to increase the margin of safety[305].

Given that the development of SCR devices is still in its infancy, we are aware of only one registered clinical trial by Borton et al using bi-directional epidural electrical stimulation to record and stimulate the spinal cord in patients with SCI[196]. However, adapting existing spinal cord stimulator devices implanted for pain in existing patients to perform a recording function, proof-of-concept recording studies have been performed[63] in clinical patients[63].

### 4.8 Ethical and regulatory considerations

As high fidelity neuroprosthetics make the leap from science fiction to clinical use, the ethical issues surrounding the ability to interact with neural systems will gain greater prominence as it enters public discourse. Chiefly, ethicists are concerned about brain-machine interfaces, as it provides an unprecedented ability to “read” a person’s mind, and perhaps even more concerning, the ability to “write” data and introduce new memories. These concerns are further reinforced by recent studies connecting multi-brain neural interfaces[306] to show the ability to communicate decisions with neural interfaces, prompting the Neurotechnology Ethics Taskforce to release guidelines for the responsible development of neurotechnologies[307]. In this regard, SCR has the additional advantage of better societal acceptance, as recording from the spinal cord will not violate a patient’s cognitive privacy. Nonetheless, neuroprosthetics has a profound potential to change an individual’s idea of self[308], as seen in individuals with Parkinson’s disease who become entirely dependent on their Deep Brain Stimulator devices to establish their identity[309,310]. Lessons can be learnt from the Freehand System (NeuroControl Corporation, Valley View, OH, USA) which demonstrated the ability to improve grasp function in C5-C6 lesion tetraplegic individuals[311]. Scientific success is, unfortunately, no guarantee for financial viability as a product and support for the device ceased, leaving previously satisfied individuals the unfortunate experience of being “paralyzed again” when they do not have a consistent manufacturer to service their prosthetics[312].

While neuroprosthetics promise a revolution in the treatment of SCI, the potential risks with these novel devices is unclear and regulatory agencies have a duty to protect individuals from unacceptable risks. Besides the challenges raised in this review, there are yet unknown side effects with longer implantation of spinal cord interfaces, including intractable pain from electrical discharge that cannot be rectified, as well as deficient data on long-term effectiveness, and enhancements have been suggested to the Federal Drug Administration’s existing processes[313] to introduce stringent post-market surveillance for neuroprosthetic devices. Recognizing the need for specialized regulation, the FDA has released a draft guidance document specifically for Brain-

Computer Interfaces, setting standards for device components such as leads, connectors, electrodes and batteries[314]. At the same time, neuroprosthetics could represent the only opportunity for individuals with SCI to regain function with no suitable alternatives, and this is where programmes such as the FDA Breakthrough Devices Designation allow an opportunity for regulatory issues to be efficiently addressed and the access to market expedited safely[315].

### 5.1 Vision: Spinal cord bioelectronic bypass

The confluence of advances in flexible multielectrode interfaces, signal decoding and biological modulation has enabled recording from neural interfaces at an unprecedented scale and duration. Next-generation SCR devices will incorporate soft, flexible electronics[316] to minimize the degree of insertion trauma as well as chronic stiffness mismatches. The emergence of PEDOT as a low impedance coating[317] will improve signal acquisition while its flexible characteristics allow for arrays that can conform to the spinal cord surface. The acquired motor volition signals can be decoded, either via thresholding or spike sorting methods, as control signals for downstream spinal cord stimulators, allowing for the implantation of closed-loop spinal cord bioelectronic bypasses. Advances in power distribution and wireless charging[258] will also increase the acceptance of these devices as viable treatment options for SCI.

We believe that direct spinal cord bioelectronic bypass has potential as a neuroprosthetic treatment strategy in patients with SCI, decoding the rich motor information from multiple volitional and regulatory circuits in the brain. At the same time, this strategy avoids the need for cranial surgery and the problems with cortical motor recording such as distributed representation. There are also advantages over current open-loop neuromodulation approaches[10] or closed-loop devices triggered by inertial moment units[9] as SCR can potentially translate the patient's motor volition into movement command signals based on animal studies[65,104], leading to physiological restoration of motor intent. This potentially creates a low-latency communication between motor intention and actuated movement, which can improve rehabilitation outcomes[318] and influence cortical reorganization to compensate for motor impairments[319].

For spinal cord neuroprosthetics to be safely used in patients who are interacting with the environment, the ability to stop movement in response to dangers such as passing vehicles is crucial. Ideally, these stop signals should have a minimal error rate of environmental threat detection and incorporate inputs from internal and external sources to respond to various threats. Whilst Prasad and Sahin have demonstrated that movement timing can be decoded from SCR[103], the error rate of SCR in decoding motor states has not been objectively studied or developed for it to solely function as stop signals in neuroprosthetics for motor restoration. Until a robust strategy to generate stop signals can be developed, users of neuroprosthetics for motor restoration should limit their activities to safe environments, relying on user-controlled interfaces such as smartwatches[320] to start and stop movement algorithms.

Beyond transmission of volitional motor intention, spinal cord bioelectronic bypass approaches have the potential to become bidirectional devices, as ascending sensory signals can similarly be decoded and stimulated above the site of injury. The restoration of touch represents another goal of neuroprosthetics in SCI and recent brain interfaces have demonstrate the ability to evoke cortical sensory areas to provide feedback to stimulated hand grip[321]. Similar to the complexity of cortical motor circuits, there is increasing interest in the multisensory integration that occurs in the brain[322] as well as the diverse areas involved, implying that simple electrical stimulation of a select sensory

area may not be able to represent the sensory spectrum ranging from fine touch to temperature. In the spinal cord, the dorsal column is topographically distinct from the spinothalamic tract, providing an opportunity for separate bioelectronic bridging of these sensory modalities for a more complex representation of peripheral touch. The ability to record proprioceptive information will also provide an additional dimension to the prediction of limb position for accurate sensorimotor control, aided by the use of neural networks to improve our understanding of the sensorimotor interactions in behaviour generation[323]. Incorporating sensory feedback into efferent motor activity requires complex computations[324] that take into account the conduction delay in sensorimotor conduction, as well as uncertainties present in sensory interaction with the environment. Additionally, the transformation of the descending motor command to endpoint movement undergoes a nonlinear process, affected by muscle properties, position and tendon properties[325].

Given the parallel advances in targeted spinal cord stimulation[9,10,326] restoring motor function in human trials, we contemplate the reasons why control signals generated from SCR devices have not been coupled with spinal stimulation to functionally bypass SCI in animal models, by evaluating the implementation of brain-spine interfaces. The group led by Gregoire Courtine has demonstrated that rehabilitation with epidural spinal stimulation (ESS) modulated by cortical signals improved the functional outcomes in rat[327] and primate[328] models. In particular, the use of cortical activity to time an ESS sequence improved gravity-assisted locomotion and even reducing fall events in simulated staircase climbing[328]. We believe a key component to the success of this strategy is the low latency between cortical signals achieved at 5ms, allowing the transmission of brain-spine information at speeds approaching physiological spinal cord conduction velocity[329]. The authors attribute it to their "ecological" approach to neural decoding[330], using summated multiunit activity to trigger stimulation, reducing the computational burden. Additionally, the simplicity of this approach allows rapid calibration to account for daily variations in neural representation. In contrast, despite adequate prediction of movement, computational latency was not reported in recent SCR studies[65,109]. This suggests that simple decoding algorithms may perform better in real-time settings for rhythmic lower-limb locomotion, at least until computational capabilities catch up with physiological demands. For more complex directed upper-limb movements, however, a dedicated mapping of signal source to target movement will be required. This increases the computational complexity and simple global spike summation is likely insufficient, requiring more complex spatial analysis approaches[331]. We expect that future studies working towards a spinal cord bioelectronic bypass will need to experiment with the complexity of decoding algorithms, striking a balance between computational demands and accurate representation of volition.

### 5.2 Conclusion

Recording neural signals directly from the spinal cord enable decoding of motor volition and improvements in electrode materials, especially with flexible designs and low-impedance electrode coatings, will allow for safer implantation, better signal acquisition and reduced FBR. To translate SCR to clinical use in SCI neuroprosthetics, further studies into the ability of SCR to decode motor intent with long term use are required. When used in a closed-loop neuroprosthetic device in SCI, recording from the spinal cord can potentially sample integrated motor signals from multiple regions in the brain, allowing for a comprehensive representation of motor volition. Spinal cord interfaces can potentially function as bidirectional systems, transmitting sensory data to the uninjured spinal cord above a site of injury. Clinical challenges must be considered systematically before spinal cord interfaces can be safely deployed in individuals with SCI. These challenges are likely to be faced by

the pioneering neuroprosthetic devices entering SCI human trials[196,197] but lessons acquired from the implementation of spinal cord interfaces in larger cohorts will serve to improve future device permutations. We envision that SCR will form an integral component of next-generation spinal cord interfaces, allowing for the real-time decoding of motor volition and sensory data for truly closed-loop spinal cord bioelectronic bypasses, irrevocably altering the paradigm of SCI prognostication and management.

## Review criteria

Scopus (Elsevier), Web of Science (Clarivate Analytics) and PubMed (United States Library of Medicine) were searched for articles published in English from the start of publication to 25 June 2021. Search terms included “neuroprosthetics”, “bioelectronics”, “brain-machine interface”, “brain-computer interface”, “neural interface” and “spinal interface” specific to the “spinal cord” and applied in a “recording”, “sensing” or “reading” capacity. Abstracts were filtered to focus on devices used in spinal cord recording followed by a review of the articles and their relevant references.

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