A Review of Cell Therapies and Neural Interfaces in the Treatment of Spinal Cord Injuries: Recent Progress and Future Perspectives

Brooke Decker*

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Abstract

Spinal Cord Injury (SCI) causes neuron loss and axonal degeneration at the injury site, resulting in a loss of motor and sensory functions caudal to the point of injury. As of now, there is no successful treatment for severe spinal cord injuries to restore pre-injury functionality. Recently, researchers have been experimenting with cell therapies to regenerate axons damaged by SCI. Other therapies such as neural interfaces have been explored as methods to stimulate and strengthen axons. In conjunction, these treatment options demonstrate promise in restoring motor and sensory functions compromised by SCI. This review provides an overview of various cell therapies as well as two modalities of neural interfaces and how they may work together to treat SCI.

1 Introduction

The spinal cord functions as a communication pathway between the brain and the peripheral nerves, enabling movement and sensory functions [Sil14]. A Spinal Cord Injury (SCI) occurs when the spinal cord's communication functionality is compromised, either temporarily or permanently, leading to the loss of motor and sensory functions [Ahu17] [Ala16].

The spinal cord is organized into two regions: grey matter and white matter. Grey matter contains neuronal cell bodies and is primarily responsible for processing and cognition. In contrast, white matter consists of myelinated axons [Ahu17] [Fie08]. Axons are the fibers that extend from a neuron, and they allow nerve cells to send electrical and chemical messages to other nerves, glands, and muscle cells. A myelin sheath is a fatty layer that surrounds and insulates each axon that helps transmit signals over long distances. Accordingly, white matter is mainly responsible for coordinating communication between different brain regions by regulating and distributing neuronal signals produced by the

*Advised by: Dr. Eshann Rao, PhD

grey matter [Ahu17] [Fie08]. Furthermore, white matter comprises ascending tracts, which transmit information to the brain, and descending tracts, which relay information from the brain to the periphery [Sil14] [Ahu17]. For example, an ascending tract relays sensory information (like pain or temperature) to the brain for processing, while a descending tract relays motor information (like instructions to move an arm or leg) from the brain to the appropriate peripheral nerves [Ahu17].

While the spinal cord and the brain comprise the Central Nervous System (CNS), nerve fibers extending off the spinal cord from the Peripheral Nervous System (PNS). The CNS and the PNS work together to maintain motor, sensory, and autonomic functions [Hol17]. SCI affects the neural tissue, which disrupts the communication between the CNS and PNS, resulting in complete or partial loss of sensory and motor function caudal to the point of injury [Ahu17]. Unlike the PNS, nerves in the CNS rarely recover after damage [Hol17]. As a result, the phenotypes of SCI include paraplegia (incomplete or complete lower-limb paralysis) and quadriplegia (both upper and lower limb paralysis) [Ala16].

There are two causes of SCI: non-traumatic and traumatic injury. Non-traumatic SCI occurs when an acute or chronic disease process, such as a tumor, infection, or degenerative disease, causes the SCI. In contrast, a traumatic SCI occurs after a dramatic physical impact, like a fall, automobile accident, or sports-related injury [Ahu17]. The severity and location of the injury determine its extent [Ala16].

SCI breaks down further into two phases, the primary and the secondary. The primary phase constitutes the initial impact coupled with persistent compression. Elements responsible for this can include penetrating foreign objects, bone fragments, hematoma, and shock waves, resulting in the complete or partial disruption of spinal cord connectivity [Sob10]. Initiated by the primary phase, the secondary mechanism of SCI is marked by a robust pro-inflammatory response, continuing for several days or months after the initial injury [Ahu17]. The secondary phase encompasses a cascade of biochemical and cellular processes which cause ongoing cellular damage, cell death, axonal loss, and demyelination. In turn, the micro-environment at the point of injury inhibits axonal regeneration and results in limited neuroplasticity [Kab10] [Sob10]. In other words, the nerves cannot grow back.

As of yet, there is no treatment available that completely restores the injury-induced loss of functionality. Current therapies for SCI shortly after injury include surgical interventions and the use of high-dose methylprednisolone. Long-term treatment strategies for SCI necessitate rehabilitative care [Sil14]. Surgical interventions intend to re-establish spinal stability, realign the spinal column, and decompress the spinal cord to minimize the effects of both the primary and secondary injury [Sil14] [Ahu17]. These procedures involve reducing built-up pressure from injury-induced swelling and stabilization via instrumented fusion like implanted metal hardware [Ahu17]. Moreover, intravenous high-dose methylprednisolone, a potent anti-inflammatory agent, serves as a neuroprotective agent in treating SCI [Ahu17]. Therefore, intravenous high-dose methylprednisolone aims to protect nerve cells against damage, degener-

ation, or impairment of function by limiting the inflammatory response of the body [Sil14] [Ahu17]. The currently approved treatments described above only manage symptoms associated with SCI without producing beneficial clinical outcomes. Thus, the effects of SCI are predominantly permanent, with current treatments incapable of restoring the partial or complete loss of motor, sensory and autonomic functions [Sil14].

While there is currently no cure for SCI that can meaningfully restore lost motor function and injured axons, several promising therapeutic strategies are being pursued, including cell therapies and neural interfaces.

One potential treatment for SCI is cell therapies. In particular, cell therapies entail the use of various stem cells and progenitor cells. Stem cells have the ability to self-renew, proliferate, and differentiate into multiple cell types [Kab10]. Progenitor cells are similar to stem cells but differentiate into a few specific types of cells [Gle21]. In treating SCI, cell transplants into the site of injury can provide trophic support, neuroprotection, and anti-inflammatory effects, as well as encourage long-distance axonal regrowth [Ash19]. The cell therapies discussed in this review can potentially address various challenges in treating SCI, including reconstituting neural cells, re-establishing an environment conducive to axonal regrowth, and restoring long-distance axonal connections. The cell types include Embryonic Stem Cells (ESC), Induced Pluripotent Stem Cells (iPSC), Mesenchymal Stem Cells (MSC), Schwann cells (SCs), and Olfactory Ensheathing Cells (OECs). When combined, each cell can potentially address specific aspects of the SCI to promote axonal regrowth.

Another potential treatment for SCI utilizes neural interfaces like Functional Electrical Stimulation (FES) and Brain-Machine Interface Technology (BMI) to stimulate and strengthen axons to improve neural signal transmissions. BMI technology recognizes user intent by measuring brain activity and translating it into executable commands usually performed by a computer [Ban21]. In contrast, FES is a methodology that uses short bursts of electrical pulses to generate a muscle contraction. Notably, FES relies on intact motor neurons for muscles to receive the command to contract [Pop01]. When used in conjunction, BMI and FES can bypass the point of injury to send cortical commands to the appropriate descending motor pathways [Ala16]. The neural bridge created in this process acts as an avenue for motor commands to overcome SCI and initiate tangible muscle movement [Ala16]. The connection can also act as an ascending tract, providing sensory feedback to the brain. The two-way connection or closed-loop is advantageous as a treatment for SCI as it reinforces neuronal plasticity and provides promise in rehabilitating both motor and sensory functions [Jac12] [Ala16].

This literature review aims to assess potential treatments of SCI involving the intersection of cell therapies and neural interfaces. Summarized here is a comprehensive review of the emerging fields of cell therapies and neural interfaces and how they may intersect and work together to treat SCI.

2 Cell Therapies

Cell therapies address various facets of SCI, as SCI is a complex and multifaceted injury [Sil14]. The injury process includes the direct transection of neurons, inflammatory responses that instigate axon retraction, inflammatory mediated death of oligodendrocytes (causing loss of myelination), and the stimulation of mediators which prevent axonal reattachment. Additionally, axons that do not retract, proximal to the site of injury, still develop abnormalities like the loss of myelination and swelling of the axonal body, both reducing the excitability of the region [Ich10] [Nas01]. Cell therapies may remedy the lack of axonal regeneration and minimal functional recovery observed after SCI by replacing neural cells lost after SCI or promoting axon regeneration and neuroprotective effects [Sil14].

2.1 Cell Types

This section discusses the functional benefits and concerns of emerging cell therapies to treat SCI. Specifically, the cells include Embryonic Stem Cells (ESCs), Neural Stem Cells (NSCs), Induced Pluripotent Stem Cells (IPSCs), Mesenchymal Stem Cells (MSC), Schwann Cells, and Olfactory Ensheathing Cells (OECs).

2.1.1 Embryonic Stem Cells and Induced Pluripotent Stem Cells

ESCs are a type of pluripotent stem cell capable of differentiating into various cell types [Ich10] [Lim06]. ESCs can replicate indefinitely and differentiate into all three primary germ layers cell lines that eventually formulate all cell types in the body, as they originate from the inner cell masses of early embryos. Thus, human ESCs are considered an abundant source of pluripotent stem cells [Ich10] [Jon03] [Lim06].

In potentially treating SCI, ESCs function to promote neural regeneration and remyelination by reconstituting neurons and white matter. In particular, previous studies have demonstrated that transplanted ESCs can promote the remyelination of damaged axons [Sil14] [Zha10]. This effect is achieved first in culture by inducing the differentiation of ESCs into neurons and oligodendrocyte progenitor cells (OPCs), which produce the myelin sheath insulating neuronal axons before being implanted into the affected SCI area [Son07] [Zha10]. For example, OPCs implanted in myelin-deficient shiverer mice differentiated in mature oligodendrocytes, restoring myelination [Nis05] [Sil14]. Similarly, Keeristead et al. demonstrated that the transplantation of OPCs, derived from human ESCs, led to remyelination and locomotor functional recovery in rats with SCIs [Kei05] [Sil14] [Zha10]. Also, Deshpande et al. demonstrated the potential of ESCs restoring functional motor units by exploring the potential of motor neurons derived from ESCs to replace those cells destroyed in paralyzed adult rats functionally [Des06] [Zha10]. However, ethical, moral, and religious limitations present hindrances to the use of ESCs in research and medicine.

iPSCs are an alternative to ESCs, which are functionally similar while presenting substantially fewer ethical limitations, as they originate from skin or blood cells that have been reprogrammed back into an embryonic-like pluripotent state [Zac09]. Additionally, iPSCs present a reduced risk of immunological rejection and, therefore, may be more useful in clinical regenerative therapies [Li13] [Tak06]. IPSCs can generate three main neural cell types (in vitro), including functional neurons, astrocytes, and oligodendrocytes [Li13] [Miu09].

Similar to ESCs, iPSCs can restore function and promote axonal remyelination. For example, two experiments from the Okano lab showed that NSCs derived from iPSCs implanted in immunocompromised contusion mice lead to trilineage neural differentiation and functional recovery, all in the absence of tumor formation [Nor11] [Tsu10] [Sil14]. Furthermore, Fujimoto et al. transplanted long-term iPSC-derived Neural Stem Cells (NSCs) into the site of SCI to verify the long-lasting effects of the iPSC-promoted functional recovery. The grafted cells enhanced remyelination, axon regeneration, and the survival of endogenous neurons [Fuj12] [Li13].

In addition to the ethical challenges associated with ESCs, both cell types possess disadvantageous attributes. For both ESCs and iPSCs, similar concerns of oncogenesis and allodynia limit their use. Oncogenesis, or cancerous tumor formation, is cause for concern because of stem cells' potential to divide uncontrollably [Ich10]. Thus, the neuronal growth caused by ESCs and iPSCs can lead to tumor formation, posing concerns regarding the safety of the cell types [Li13] [Tak06]. Additionally, the development of allodynia, an abnormal sensation to a routine stimulus, has become a concern due to the potential formation of improper nervous connections [Ich10] [Mac06]. Thus, additional studies are required to confirm the safety and feasibility of ESCs and iPSCs in treating SCI.

Nevertheless, both ESC and iPSC-derived Neural Stem Cells (NSCs) exhibit consistent characteristics such as continuous expandability, stable neuronal and glial differentiation ability, and the capacity of generating functional mature neurons in monolayer culture. The efficacy of neural regeneration and neuronal function promotion observed in a variety of ESC and iPSC NSC applications has made these cells promising therapeutic options in the treatment of SCI [Li13].

2.1.2 Mesenchymal Stem Cells

MSCs may also have therapeutic promise for SCI, as they are multipotent cells that can differentiate into distinctive end-stage cell types. Independent investigators have shown that MSCs give rise to neural-like cells (neurons and glia) both in vitro and in vivo [Son07].

MSCs function to provide trophic support and promote axon regeneration and sprouting in potentially treating SCI [Ash19]. MSCs are a promising cell source for repairing a CNS injury because of their many beneficial effects. For example, MSCs have an anti-inflammatory effect, attenuate myelin loss, and provide trophic support, molecules that allow neurons to develop and maintain connections with their neighbors. As a result, MSCs promote axon regeneration

and sprouting. In addition, MSCs are anti-apoptotic and angiogenic, meaning they do not give rise to tumors, and autologous (self-to-self) transplants of MSCs can occur [Ash19] [Feh11] [Sil14]. Another appeal of MSCs is because they are easy to isolate and expand without severe technical and ethical problems [Sil14]. Several studies have shown that the transplantation of MSCs in SCI animal models promotes sensorimotor function recovery, neurotrophic paracrine effects, and posttrauma inflammation regulation. For example, Nakajima et al. demonstrated that the transplantation of MSCs regulates the activation of macrophages, which trigger defense systems, in the post-SCI inflammatory environment [Li13] [Nak12].

The collection source of MSCs determines the attributes of each type of MSCAdult or postnatal tissues, such as the bone marrow, adipose, umbilical cord, are easily an accessible and ethically sourced supply of MSC [Sil14].

One source of MSCs is from the bone marrow (bmMSCs). In preclinical experiments, the transplantation of bmMSCs in large animals demonstrates an improvement of locomotor performance. Substantially, the initial clinical trials of bmMSCs did not cause severe complications, establishing the safety and feasibility of the clinical use of bmMSCs [Sil14].

The umbilical cord (UC-MSCs) and the adipose tissue (AD-MSCs) also source MSCs. Some studies demonstrate that UC-MSCs propagate more extensively and swiftly in the injury site than adult bmMSCs, because of the more proliferative properties of UC-MSCs [Sil14] [Tro08] [Wei06]. In full transected rats, the transplantation of human UC-MSCs led to an increase in trophic factors and produced axonal regeneration across the injury site [Sil14] [Yan08]. Additionally, the implantation of UC-MSCs induced a lesser immune response and caused less graft rejection than other stem cells. As for MSCs derived from the adipose tissue (AD-MSCs), subcutaneous areas source AD-MSCs with minimally invasive techniques such as liposuction. AD-MSCs have been shown to secrete trophic growth factors, modulate activated immune cells, have an anti-apoptotic ability, and have a multilineage differentiation capacity [Ash19]. Like UC-MSCs, authors have also claimed that AD-MSCs have a higher growth rate when compared to bmMSC [Ker06] [Sil14]. In in vivo experiments, functional recovery was achieved by transplantation AD-MSCs in a contusion SCI rat model [Sil14] [Zha09]. Overall, the transplantation of MSCs results in the modulation of inflammation, axonal regrowth, reduction of the glial scar, support for remyelination [Sil14].

Although the benefits of MSC use are extensive, there are some challenges. These include the low survival rate of grafted cells (5–10%), the lack of neural differentiation, glial scar formation, cystic cavity formation, the inhibitory cellular environment, the transplantation time point, and the graft/host immune responses [Li13]

2.1.3 Schwann Cells

Schwann cells (SCs) are cells of the peripheral nervous system whose main function is to produce the myelin sheaths that surround the PNS axons and

promote axonal growth after injury [Ich10]. For example, after an injury in the PNS, Schwann cells promote axonal regeneration by secreting growth factors and expressing molecules that support axon growth [Sil14].

In potentially treating SCI, the implantation of Schwann cells could provide trophic support and serve to promote axon regeneration and remyelination [Ash19]. For instance, Takami et al. demonstrated that SCI animals implanted with SCs led to functional recovery, reduced cavitation, and the extension of spinal axons into grafts, many of which are myelinated [Tak02] [Sil14]. Additionally, others have observed that the implantation of SCs causes extensive infiltration of endogenous SCs to the site of injury [Hil06] [Sil14], suggesting that SCs may contribute to the recovery observed in other therapies. Moreover, studies have observed SCs to be safe and feasible while promoting remyelination [Hal02] [Sil14].

As suggested above, SCs are limited when used in isolation. Studies have found that the migration of SCs into the CNS halted after contact with astrocytes [Shi00] [Sil14]. Additionally, the corticospinal tracts were delayed and had poor regeneration activity following SCs transplantation [KF05] [Sil14]. SCs transplants also do not allow axons that enter grafts to exit and reenter the host spinal cord [Pin01] [Sil14]. To put this in perspective, SCs create a one-way road. They encourage the traffic to enter but do not allow it to leave again; it is effectively a cul-de-sac [Rai01].

In response to these limiting factors, studies have combined SCs with other treatment methods like neuroprotective agents, blockers of inhibitory molecules, or neurotrophic factors [Sil14]. The positive therapeutic outcomes observed as a result of SCs in combination with other treatment protocols suggest that SCs work best when used in conjunction with other strategies that minimize the inhibitory nature of the lesion site.

2.1.4 Olfactory Ensheathing Cells

Olfactory Ensheathing Cells (OECs) are a particular type of glial cell that ensheath the non-myelinated axons of olfactory neurons and are silimar which Schwann cells ensheath non-myelinated peripheral neurons. They also share the property of assisting axonal regeneration. Unlike Schwann cells, OECs can penetrate the surface of the CNS and repeatedly migrate from the PNS to the CNS [Rai01]. Therefore, going back to the cul-de-sac analogy, OECs are a through-street. In combination, several studies have OECs and SCs to cause additive therapeutic effects [Ich10].

Olfactory nerves are the source of OECs in the body. These olfactory nerves are sensory nerves that function for the sense of smell and are a population of adult neurons that continually renew throughout life [Rai01]. Because of this, OECs are prime candidates for SCI treatment: the nerves continually renew, and OECs can continually regenerate new axons while performing remyelination. After being obtained through nasal biopsies, OEC implantation can occur either immediately or later. With more time, the cells are dissociated and cultured into sufficient cell numbers [Fé05] [Lim06] [Sil14].

In potentially treating SCI, OECs provide trophic support as well as promote axon regeneration and sprouting. Ramon-Cueto and colleagues demonstrated the regeneration of corticospinal axons and improvements in animal motor behavior after implantation of OECs into a complete thoracic transection injury model [RC00] [Sil14]. Additionally, studies have shown that OECs promote corticospinal regeneration and functional recovery in discrete and chronic SCI models [KF03] [Li13] [Sil14]. Other studies have observed improved function in chronic and acute SCI animals, with incomplete and complete lesions, using Xeno and allotransplant OECs [Sil14]. Tetzlaff et al. report that approximately two-thirds of the experimental studies demonstrated improvements in behavior outcomes [Tet11].

Although OECs present as an attractive candidate in the treatment of SCI, OECs have their disadvantages. Notably, a significant number of experiments transplanting OECs in SCI models have failed to demonstrate any therapeutic action [Sil14].

2.2 Combination of Cell Therapies

Each cell has individual advantages and disadvantages in the treatment of SCI. However, when used in conjunction, the different cell therapies can address specific aspects of the SCI to create an environment conducive to axonal regrowth and promote axon regrowth. In addition, the strengths of one cell's abilities can support another's weaknesses.

As a reminder, SCI consists of an initial mechanical injury and a secondary injury caused by the body's inflammatory response. The second injury creates an environment unconducive to axonal regrowth, while the first injury initiates cell death. Thus, to regrow axons, an adequate anti-inflammatory environment must be achieved first.

MSCs and neural stem cells derived from ESCs or iPSCs can induce an environment conducive to axonal regrowth by providing trophic factors and chemokines, which create an anti-inflammatory effect. The addition of ESCs and iPSCs differentiated into neurons can then promote neuronal regeneration. Also, the implantation of oligodendrocytes, which produce the myelin sheath-insulating neuronal axons derived from ESCs and iPSCs, can promote remyelination. MSCs, SCs, and OECs can provide trophic support to promote and sustain axon regeneration and sprouting.

To summarize, the implantation of ESCs, iPSCs, MSCs, SCs, and OECs have their own individual promise in poetically treating SCI. Strategies for the therapeutic use of stem cells and their derivatives in spinal cord injury (SCI) include cell replacement, trophic support, and facilitation of axon regeneration. When used in conjunction, the cells can address all facets of both the primary and secondary injury to regrow axons to the fullest extent potentially.

3 Neural Interfaces

Neural interfaces present a different approach to treating SCI by stimulating and strengthening axons [Ala16]. This section discusses two neural interfaces: BMI and FES. These neural interfaces monitor, decode and manipulate neural activity by invoking activity-dependent plasticity mechanisms for therapeutic benefit [Jac12]. For example, FES of the spinal cord and muscles aids in retraining motor circuits and improves residual capabilities in patients with SCI by strengthening the efficacy of axons in signal transmission [Pop01]. In contrast, BMI decodes motor intentions from cortical signals enabling patient-driven control of assistive devices such as computers and robotic prostheses [Jac12]. In conjunction, BMI technology and FES bypass the injury site to communicate cortical commands to appropriate descending motor pathways. In doing so, the neural bridge communicates movement commands intended by the brain to induce the functional movement of a once paralyzed limb [Ala16] [Jac12]. The following sections discuss these topics in greater detail.

3.1 Brain-Machine Interface

BMIs record and decode signals from the brain to enable volitional control of assistive devices and modify cortical activity patterns in an individual with an SCI through neurofeedback [Jac12]. This section summarizes different approaches to recording neural signals, the motor intent decoding process, and applications of BMI in computer-based neuroprosthesis.

3.1.1 Neural Recording Modalities

BMI first requires recording neuronal signals related to movement and movement intention, signals that would usually travel down the spinal cord without an SCI [Ala16]. Neuronal signals are the tiny electrical signals which neurons use to communicate with each other. More specifically, these signals are discrete events whose rate and timing carry information [Ben14]. In BMIs, these are recorded and decoded for intentions of movement [Ala16]. For example, a particular behavior relies on the distributed and coordinated activity of particular neural populations, which communicate their intent through neuronal signals [Pan15]. Neuronal activity is detected using a range of techniques, including optical, magnetic, and electrical recordings [Ala16].

This review focuses on three such techniques, including the electrical recording methods of Electroencephalography (EEG), Electrocorticography (ECoG), and penetrating electrodes. Generally, as neural recording devices become more invasive, the resolution and accuracy of the transmitted information increases.

EEG records the neuronal signals from a population of underlying cortical neurons through non-invasive electrodes placed on the scalp [Ala16] [Buz12]. The non-invasive nature of an EEG makes it a readily accepted form of neural signal acquisition in humans and allows for the stable recording of neuronal signals over a long period. Although, the reduced invasiveness of EEG causes

the resolution and accuracy of information to be limited. For example, the cranium and skin dampen neuronal signals due to the placement of electrodes on the scalp [Ala16] [Mak09] [Buz12]. Additionally, ambient artifacts and noise contaminate EEG recordings due to the placement of electrodes on the scalp. Thus, the neural signal quality of an EEG is limited in its effectiveness in detecting neuronal intent. Accordingly, EEGs have faced scrutiny for their slow translation of motor intent in real-time [Ala16] [Mak09].

ECoG records population neural activity by the invasive placement of electrodes on the exposed cortex (either epidurally or subdurally). As a result of the invasivity, ECoG localizes its neuronal signal recording, improving its signal accuracy compared to EEG [Ala16] [Buz12] [Tha13]. Specifically, ECoG captures a high signal-to-noise ratio, improving signal quality and specificity aswell as nueral translation speed. On this account, ECoG is an effective controller of neuroprostheses [Ala16] [Fif12]. For example, ECoG-based BMI has proven highly effective in performing fine motor tasks of prosthetic limbs in paralyzed humans and nonhuman primates [Ala16]. Moreover, the conservative invasivity of ECoG, placement on the surface of the brain and not deeper, allows for the stable recording of neuronal signals over a long period. However, the invasivity of ECoG has its limitations. For instance, clinical applications of ECoG require a craniotomy to implant electrodes; thus, the use of this neural recording modality is limited to patients amenable to surgery and justified in the risk-to-benefit ratio of surgery [Ala16].

Penetrating electrodes record signals from an individual neuron or an ensemble of neurons proximal to the electrodes' placement inside the brain parenchyma. Through their invasive placement, these micro-electrodes are afforded a high signal-to-noise ratio and improved signal accuracy because of their capability to record from individual neurons or small neural populations. However, penetrating electrodes initiate an immune response because their implantation pieces the blood-brain barrier [Ala16]. As a result, penetrating electrodes face limitations to their biocompatibility and longevity due to scar tissue formation. To be specific, an encapsulation layer of glial cells forms around the electrodes, giving rise to electrode impotence that deteriorates the signal accuracy of the electrodes over a matter of weeks or months [Ala16] [Pol05] [Cog08]. Thus, penetrating electrodes are too invasive to achieve stable recordings over time, unlike the non-invasiveness of EEG and ECoG. Furthermore, the rigidity of penetrating electrodes makes them susceptible to displacement from the original recording site due to brain micromotion, causing a loss of the original neural signal [Ala16] [Cog08] [Gil06]. Therefore, to attenuate the limitations of penetrating electrodes, advances in the field of biomaterials are necessary, namely, the discovery of flexible biomaterials that are robust to brain micro-motion and can prevent gliosis [Ala16] [Leb11]. An unresolvable limitation is the invasive nature of penetrating electrodes. The implantation of electrodes requires a craniotomy in clinical applications and the placement on brain matter. Consequently, similar to ECoG, only patients amenable to surgery and its inherent risks could consider this neural recording modality [Ala16].

As summarized above, electrophysiological recording techniques (EEG, ECoG,

or penetrating electrodes) differ in their invasiveness and subsequent signal accuracy. Each technique has its advantages and limitations in its ability to record neuronal signals. Nevertheless, the neuronal signals detected by each neural recording modality can direct neuroprostheses for SCI patients [Ala16] [Ben14].

3.1.2 Decoding Motor Intent

BMI can translate neural signal recordings from the brain into digital commands to control an external prosthesis in real-time [Ben14]. The motor intentions originate from the decoding of neural signal recordings [Ala16].

In the recording process, BMI electrodes are usually positioned in well-defined micro-stimulation mapped brain regions. Examples include the frontal and parietal regions of the brain, which mediate movement intention, modulation, and execution, and the anterior intraparietal area and ventral premotor cortex, which mediate grasping in primates [Ala16].

A BMI further narrows its scope of motor intentions by decoding the specific populations of neurons that are activated when a subject intends to move an arm one way versus another, as neurons are direction-dependent. In other words, neurons tuned to an intended direction start firing more than others tuned to different directions [Ala16] [Geo86]. Information extraction from these directionally-tuned neurons is crucial in constructing BMI-driven neuroprostheses [Ala16] [Sch06] [Wal09].

A computer decodes the motor intent signals to execute external actions in a neuroprosthesis by associating imagined intents with different frequencies such as (8–12 Hz), beta (12–30 Hz), and gamma (30–100 Hz) [Ala16] [NA12]. Generally, the decoding algorithm calibrates to an individual using neural signals collected during the performance of a predetermined set of real or imagined arm movements. The framework of the decoder is adjusted accordingly, so the output of the algorithm best predicts the direction of the intended movement. After this calibration process, individuals with SCI can use the decoder for the real-time control of a device via the brain [Jac12].

Notably, during this latter process, the user receives feedback from the effector, such as a computer cursor or robotic arm. As a result, patterns of neural activity change as the user masters the interface [Jac12]. In response, individuals learn volitional control of a feedback signal that relays real-time information about specific brain activity in a process known as neurofeedback training [Bir07] [Jac12]. For example, previous punishment-reward-based behavior studies have demonstrated that monkeys have the ability to increase the firing rates of individual cells to operate a device that controls reward delivery [Fet69] [Jac12]. Subsequent BMI experiments have found that a significant reorganization of cortical activity occurs following practice with BMI devices. In particular, changes in the directional tuning of neurons used by the decoder as well as reduced modulation of neighboring neurons occur [Jac12]. The process of learning to control BMIs also entails changes in the underlying brain signals, including increasing amplitudes of slow cortical potentials or the sharpening of brain waves sensorimotor-rhythm topographies [Bir99] [Buc08] [Jac12] [McF10].

The neurofeedback from BMI can be used after an injury to alter functional connectivity and normalize patterns of cortical activity [Enz08] [Jac12] [Vá12].

3.1.3 External (computer-based) Neuroprosthetics

Many studies have found BMI as a definitive ability to restore volitional control to individuals with an SCI via the manipulation of assistive devices such as a robotic arm or computer cursor [Ala16] [Jac12]. BMI attempts to restore a patient's mobility by translating neural signals into commands that can operate devices integrated into a patient's environment, such as a robotic arm or power wheelchair. BMI allows patients to regain a degree of autonomy lost at the onset of their injury [Ala16].

For example, a quadriplegic patient successfully controlled a high-performance prosthetic arm by only using thoughts. The patient achieved an impressive success rate of 91.6% in a three-dimensional target-based reaching task using an advanced robotic arm with seven degrees of freedom [Ala16] [Col13]. Additionally, after the implantation of an invasive microelectrode array in a young man with C3-C4 quadriplegia, he utilized BMI to operate a 2D computer cursor, perform simple actions with a robotic arm, and control the grasping movements of a prosthetic hand [Hoc06] [Jac12]. Research progressed six years later when the modified BMI system enabled the control of 3D reaching and grasping of robotic arms in two paralyzed patients after experiencing a brainstem stroke [Hoc12] [Jac12]. In a similar study, one patient was able to use the robotic arm to drink through a straw from a bottle, demonstrating the future practicality of BMI systems for activities of independent daily living [Jac12].

The neural control of robotic devices, prostheses, and software interfaces granted by BMI technology can allow patients to regain control over certain aspects of their everyday lives, enabling patients a greater degree of influence and interaction with their environment than their deficits would typically allow. The controlling of external devices allows individuals with SCI to take back some of their lost functions [Ala16].

Overall, BMIs allow for the voluntary control of assistive devices by individuals with SCI via recorded neuronal signals. An algorithm decodes neuronal signals into motor intent commands for a device such as a robotic arm to execute. These electronic devices allow individuals to regain control over certain aspects of their lives affected by the SCI [Ala16] [Jac12].

3.2 Functional Electrical Stimulation

Another neural interface, FES, refers to the electrical stimulation of motor neurons via surface or implanted electrodes to elicit a muscle contraction [Pop01]. In general, FES can elicit specific motor movements using a specific stimulation sequence. FES has become a widely adopted practice in rehabilitation training after SCI due to its therapeutic benefits [Luo20]. This section summarizes different approaches to electrical stimulation of the spinal cord designed to restore motor function to individuals with SCI. Specifically, the following section

discusses the types and benefits of FES.

3.2.1 Types of Stimulation

There are three methods of spinal cord stimulation for the restoration of movement after a paralyzing SCI: transcutaneous, epidural, and intraspinal [Iev17]. Similar to the neural recording modalities of BMI, the difference between the stimulation methods of FES is the placement of stimulative electrodes in relation to the spinal cord [Ala16] [Iev17]. Each stimulation site determines the parameters required to elicit the desired result and the neural pathways activated by the stimulation, as well as the advantage and disadvantages [Iev17] [Sha14].

Transcutaneous stimulation involves the application of low-voltage electric currents to the skin surface above the vertebral column to improve motor function after injury [Iev17]. The electrode placement on the skin means that the electrodes are non-invasive, have lifetime biocompatibility, and are recyclable. In particular, the electrodes involved in this modality have the most prolonged electrode function and biocompatibility of the other two methods described below [Ala16]. It is important to note that transcutaneous stimulation acts as a neuromuscular stimulant, whereas other more invasive methods rely on the spinal cord to first be stimulated in order to stimulate the muscles [Ala16] [Iev17]. Transcutaneous stimulation relies on basic mechanisms such as increasing the baseline electrical activity to induce results. The stimulation amplifies movements induced by the stimulated region's remaining volitional motor commands [Iev17]. However, transcutaneous stimulation cannot target specific or small populations of neurons [Ala16]. Furthermore, the effects of transcutaneous electrical stimulation are dependent on the body position of an individual. For example, the current required to elicit movement is more significant in a standing position than a prone (lying down) position [Dan16] [Iev17]. Advantageously, in individuals treated with transcutaneous electrical stimulation, four out of four motor complete SCI patients had improved stepping ability on a treadmill with body-weight support and a robotic-driven gait orthosis [Ala16] [Min15]. Likewise, five out of five motor complete SCI patients regained some voluntary movement of hips and knees after transcutaneous electrical stimulation [Ala16] [Ger15]. Overall, transcutaneous approaches can be preferable as they do not require surgery. However, the novelty of this modality means that further testing of transcutaneous stimulation is needed to establish its optimal application [Iev17].

While the non-invasive nature of transcutaneous stimulation is convenient, some limitations hinder its functionality in treating an individual with SCI. For example, electrodes need to time consumingly be placed and removed with the resulting stimulation only targeting a limited number of muscles at one time [Ala16] [Iev17]. The implantation of electrodes is needed to achieve a more localized result [Ala16]. The sections below discuss implanted electrodes in greater detail.

Epidural stimulation involves electrical stimulation from surgically placed electrodes on the dura mater, the outer layer of tissue that covers and protects

the brain and spinal cord [Ala16] [Iev17]. Compared to the indefinite biocompatibility of transcutaneous stimulation, epidural stimulation electrodes are biocompatible for a shorter amount of time due to their invasiveness [Ala16]. One study of human SCI trials provides an insight into the biocompatibility of epidural stimulation. The study lasted 88 weeks, demonstrating that the electrodes remain functional for at least that long [Ala16] [Ang14]. Similar to the ECoG and penetrating electrode limitations discussed in 3.1.1, the immune response to the foreign electrodes complicates their ability to be long-lasting (relative to non-invasive modalities) in the nervous system environment [Ala16]. However, there are benefits to this invasive placement. For instance, with this method, the localization of stimulation is improved. Within the targeted areas of stimulation, the resolution is dependent on the size and number of electrodes. Nevertheless, the specificity of epidural stimulation does not reach the cellular level [Ala16]. In one study, epidural stimulation of rats and cats revealed that the depth of the epidural stimulation is limited to dorsal spinal cord structures rather than deeper ventral structures [Ala16] [Lav15]. In application, recent studies have shown the return of voluntary lower limb and hand control complete and incomplete spinal cord injuries after epidural stimulation treatments. In addition, epidural spinal stimulation enabled otherwise paralyzed people to make volitional movements in the presence of continuous, subthreshold stimulation [Iev17]. Notably, some benefits persist beyond the subthreshold stimulation, like lasting improvement in autonomic functions such as bladder, bowel, and sexual functions in both humans and animal subjects [Gad14] [Har11] [Iev17].

Intraspinal stimulation involves the use of surgically placed electrodes to penetrate the spinal cord [Iev17]. Because of its invasiveness, intraspinal stimulation studies are rare in humans, but studies of animals (cats, rats, and monkeys) still provide insights into the potential benefits of this approach. Relative to transcutaneous and epidural stimulation, intraspinal stimulation has the shortest duration of electrode functionality and biocompatibility because of its invasive nature [Ala16]. For example, in one study, intraspinal electrodes implanted cats remained only 80% functional after three months [Ala16] [Pik07]. In another study, only 67% of electrodes remained functional after six months [Ala16] [Mus00]. The localized stimulation capacity of intraspinal stimulation is by far the most comprehensive. The electrodes within the spinal cord itself allow for targeted stimulation with the highest resolution compared to transcutaneous and epidural stimulation. As a result, intraspinal stimulation can deliver stimulation to both the ventral and dorsal structures of the spinal cord, with optimal electrode lengths [Ala16]. In animal models, intraspinal stimulation can elicit various functionally relevant movements, including movements required for stepping and movements related to reaching and grasping [Iev17]. Notably, stimulation from only two electrodes sufficiently produced functional reach-to-grasp movements [Jac12]. It is challenging to predict wherein the placement of a single electrode on the cervical cord would be most helpful in producing a specific movement. Thus, a small array of implanted electrodes on the spinal cord can yield a variety of movements for several muscle groups [Jac12]. To be specific, studies have revealed that intraspinal microstimulation can induce

improvements in forelimb functions in rats, regaining their ability to extend the elbow and digits as well as the reaching and grasping functions in monkeys [Ala15] [Ala16] [Sun13] [Zim11].

Overall, the three modalities of functional stimulation described above represent the diversity of the applications and implications of FES in how they can be used to treat SCI. Each has its benefits and limitations regarding the specificity of stimulation and invasiveness. As a result of FES, the recovering voluntary motor function can improve an individual with SCI's independence and quality of life after SCI [MC20].

3.2.2 Therapeutic Benefits of Functional Electrical Stimulation

All in all, the variety of benefits observed after FES demonstrate its therapeutic potential in treating spinal cord injury motor deficits. Although FES therapy has shown significant benefits, it currently falls short of fully restoring natural movements and achieving a full recovery.

FES relies on the principle of neuroplasticity, the ability of the central nervous system to reorganize itself during the acquisition, retention, and consolidation of motor skills [Day11] [Luo20]. Through this approach, FES restores the body's ability to perform voluntary movement after SCI [Jac12]. Using a specific stimulation sequence, FES elicits specific pre-programmed motor movements, which can be controlled by unaffected body parts or incorporated into residual movements of the affected limb [Ala16] [Jac12]. This artificial electrical stimulation activates paretic muscles, reengaging the dormant neuromuscular systems below the level of injury [Ala16]. As a result, FES can facilitate the recovery of voluntary motor function in individuals with SCI [Ala16] [Jac12]. Furthermore, FES evokes lasting therapeutic effects after stimulation switches off, as the stimulation increases muscle strength, fitness, and efficacy of corticospinal transmission [Eve09] [Jac12]. Also, the recovery of voluntary motor function can improve an individual with SCI's independence and quality of life after SCI [MC20]. For example, upper-limb FES systems can enable functional grasping and limited proximal arm movement, while FES systems for lower limbs can facilitate standing, walking, or cycling [Jac12]. Overall, FES can improve respiration, circulation, hand strength, mobility, and metabolism after SCI [Luo20].

3.3 Neural Bridge

When used in conjunction, FES and BMI technologies can bypass the injury site to communicate movement from the brain to appropriate muscle groups to initiate the movement of a once paralyzed limb. As a refresher, BMI technology works to record and decode the motor intent generated by the brain [Ala16]. In this instance, FES applications could harness motor commands translated by the BMI to communicate motor commands to the body caudal to the place of injury. As a result, once paralyzed regions could execute movements in real-time. The neural bridge created in the process allows for neural information to

avoid the information blockage created by SCI [Ala16] [Jac12]. In other words, the neural bridge is an information detour that routes around the SCI.

The applications of a neural bridge device would aid different paralytic conditions caused by SCI differently. For example, paraplegia, affecting the lower limbs, impairs an individual's ability to stand and walk. Thus, in this instance, a neural bridge would aid the communication of neural signals to lower limbs [Ala16]. Quadriplegia affects both upper and lower limbs as well as the torso, inhibiting an individual's ability to reach and grasp and the ability to walk or stand. Therefore, a neural bridge would aid the communication of neural signals to upper limbs in people with quadriplegia since the focused restoration of the arms would grant them the most significant independence, and the area would be more likely to recover, being more proximal to the site of injury [Ala16]. To this end, neural bridges can potentially restore the upper-limb functions in those with quadriplegia and the lower limb functions in those with paraplegia. Summarized below are successes in using BMI and FES in combination to reanimate arm and leg movement.

Using BMI-translated neural signals, neural bridges can restore volitional arm movement in animal motor commands via the direct electrical stimulation of upper-limb peripheral nerves or muscle groups. One application of the neural bridge is the use of a Brain Machine Spinal Cord Interface (BMSCI) chip that uses BMI neural signal recordings, decodes them to motor commands in real-time, and sends appropriate electrical stimulation pulses to the intended place of movement. In this concept, the implanted chip would receive, modify, and transmit signals, bypassing the point of SCI [Ala16].

The majority of studies surrounding neural bridges thus far have focused on restoring upper limb functions in individuals with SCI, yet some recent studies have addressed the feasibility of neural bridges to restore lower-limb function as well [Ala16]. In practice, lower limb restoration is arguably more difficult than upper limb restoration because the function of walking and standing necessitates balance and reflex mechanisms which are difficult to reproduce with artificial stimulation [Ala16] [Pon13]. Another approach to the neural bridge concept addresses the balance issue by utilizing BMI technology. In this case, BMI is used to facilitate the FES of lower limbs while also controlling an exoskeleton, providing stability needed with lower-limb injuries [Ala16] [To14].

The regular use of neural bridges demonstrates promise in inducing plasticity by increasing the synaptic strength of the residual spinal neural connections across the site of SCI [Ala16] [Fet15]. In recent studies, the spike time-dependent plasticity mechanism has proven to encourage plasticity in spinal neural networks [Jac12]. For example, SCI-affected rats improved their forelimb motor function following spinal stimulation from BMI neural activity [Ala16] [Wid14].

Ideally, neural bridges would be bidirectional. In definition, bidirectional or closed-loop neural bridges induce movement from neural signals and communicate sensory input back to the brain. These cutting-edge devices would further extend the potential for neuroelectronic augmentation of injured motor circuits as well as improve the normalcy and quality of life of SCI individuals [Jac12].

To summarize, neural bridges, which combine recording and stimulation

capabilities of BMI and FES within wearable or implantable devices, could serve to replace or augment injured pathways in the spinal cord. In addition, neural pathways could induce long-term therapeutic effects by strengthening synapses, thereby inducing plasticity [Jac12]. In the future, bidirectional neural bridges could restore motor and sensory deficits in individuals with SCI.

Overall, BMI, FES, and neural bridges all share the common goal of improving the quality of life of individuals with SCI, whether through controlling external prosthesis, restoring volitional functions, or bypassing the SCI to connect the brain and the spinal cord directly.

4 Discussion of the Intersection of Neural Interface and Cell Therapies in Treating SCI

Due to the complexity of SCI, there is the expectation among researchers that combinatorial therapies will be a more effective strategy to promote recovery than a single therapeutic approach alone.

As a reminder, SCI results in the loss of nervous tissue and consequently a loss of motor and sensory function caudal to the place of injury. There is currently no cure for SCI that can meaningfully restore lost motor function, as the SCI site has limited neuronal activity and is unconducive to axonal regrowth [Sil14]. Cell therapies attempt to functionally integrate new cells into the place of injury to replace cells, provide trophic support and facilitate axon regeneration [Ash19] [Sil14]. Using BMI and FES in combination creates a neural bridge that can restore volitional functions to individuals with SCI by bypassing the SCI to directly connect the brain and the spinal cord [Ala16] [Jac12].

After an injury, the dead cells provide little infrastructure in which neural interfaces can interact. Cell therapies remedy this by adding neurons, supported by trophic factors and axon regrowth promotions, to build stimulative infrastructure in the SCI environment. After an injury, the remaining axons, on top of what might have been introduced by cell therapies, are weak. Neural interfaces remedy this by strengthening the infrastructure of the injury. Essentially, cell therapies focus on axon regrowth while neural interfaces focus on stimulating and strengthening existing axons. When combined, cell therapies can grow new infrastructure and cells while neural interfaces strengthen the existing infrastructure through stimulation. In conjunction, cell therapies and neural interfaces could potentially work to treat SCI, as they address the total sum of the problem.

The future directions of combining these therapies could include a personalized prosthesis for SCI individuals with sensory information available; on-the-go neuronal bridges to enhance the independence, quality of life, and physical capabilities of individuals with SCI; more studies surrounding the synergistic effects of multiple cell use and in conjunction with electrical stimulants like that of neuronal bridges or FES.

Overall, the combination of cell therapies and neural interfaces is a promising

approach to treat the injured spinal cord; however, more preclinical data is needed to fully understand the beneficial or detrimental effects of the individual therapies before they are used in conjunction to treat SCI.

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