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# Spinal cord repair: advances in biology and technology

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**Individuals with spinal cord injury (SCI) can face decades with permanent disabilities. Advances in clinical management have decreased morbidity and improved outcomes, but no randomized clinical trial has demonstrated the efficacy of a repair strategy for improving recovery from SCI. Here, we summarize recent advances in biological and engineering strategies to augment neuroplasticity and/or functional recovery in animal models of SCI that are pushing toward clinical translation.**

The US national SCI statistical center estimates that the annual incidence of SCI in the United States is approximately 54 cases per million people, or approximately 17,000 new cases each year[1]. The World Health Organization (WHO) approximates that between 250,000 and 500,000 people suffer from a SCI each year[2]. SCI has an immediate and devastating impact on the control of movement and many essential physiological functions. Over the past century, progress in the understanding of injury mechanisms has transformed the clinical management of SCI. Surgical procedures, supportive measures and rehabilitation protocols have improved functional outcomes and decreased morbidity in patients with SCI[2]. However, at this time no randomized clinical trial has demonstrated the efficacy of a repair strategy for improving functional recovery from SCI. Due to the limited ability of the central nervous system (CNS) to repair itself following injury, many deficits remain permanent. Half of the affected individuals remain paralyzed, with life expectancies of decades with permanent disabilities[3,4]. The estimated lifetime cost attributable to SCI ranges from US$1 to 5 million per person depending on the location of the injury along the spinal cord and its severity[1].

While a cure that could repair the injured spinal cord is unforeseeable, recent advances in biological and engineering strategies have opened promising avenues for improving function after SCI. Over the past decade, advances have occurred not only in traditional research areas such as axon regeneration, inflammation, scar formation and engraftment of neural and supporting cells, but also in the identification of mechanisms underlying spontaneous circuit reorganization, spinal cord automaticity and recovery after SCI. These new findings have redefined our understanding of requirements for restoration of function after SCI and have altered concepts regarding the design of repair interventions (Box 1). Additionally, advances in engineering have led to the emergence of a new research area — broadly termed neuroprosthetics — that leverages our understanding of motor control principles to tap into circuits and residual neural pathways spared from injury in order to enable and restore function.

Various experimental therapies are moving toward or are already in clinical trials — opening a new era for SCI medicine. Here, we review these advances in animal models, and where relevant, their translation in human patients. The majority of preclinical studies and experimental read-outs are focused on motor functions. Consequently, we primarily discuss motor recovery, but it worth noting that the recovery of autonomic and sexual functions are among the top priorities of people with SCI[3]. We first describe the main biological approaches and mechanisms for spinal cord repair. We then explain the principles through which researchers seek to use engineering strategies to enable function and augment recovery with neurotechnologies and rehabilitation. Finally, we consider the great potential, but also highlight the complexity, of combining biological and engineering approaches in order to target the multifaceted mechanisms underlying spinal cord repair and recovery.

## Biological approaches to SCI repair

Developing mechanism-based approaches to spinal cord repair will require understanding the biology of SCI lesions and of the diverse axonal growth responses that occur after injuries[5]. SCI lesions are heterogeneous in their severity and cellular organization, and both of these factors have implications for developing repair strategies. For example, anatomically complete lesions span the entire breadth of the spinal cord, thereby eliminating all neural communication across the site of transection (Fig. 1). Their repair will require restoring neural connectivity across large and hostile non-neural lesion cores, which will require invasive treatments. In contrast, anatomically incomplete SCI are formed by smaller or discontinuous lesions that spare sufficient neural tissue to support communication across the injury. Anatomically incomplete SCI are often associated with partial recovery that can benefit from strategies to augment spontaneous circuit reorganization and improve the conductivity and function of residual neural connections, including by non-invasive means.

**Diverse SCI compartments and axonal growth responses.** Regardless of their size or severity, mature lesions exhibit three tissue compartments that present markedly different cellular composition and functional interactions[5–11] (Fig. 1). Non-neural lesion cores consist of perivascular-fibroblast-derived stromal cells, meningeal fibroblasts and pericytes that proliferate in areas undergoing CNS cell death[6–8]. Reactive astrocyte scar borders formed by newly proliferated astrocytes surround non-neural lesion cores and protect adjacent functional neural tissue by corralling inflammatory cells within areas of damaged tissue[9,10]. Spared but reactive neural tissue that surrounds astrocyte scar borders contains all cellular elements

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**Box 1 | Requirements for restoration of function**

It was long assumed that recovery from SCI would require precise reconstitution of the neural connectivity present before damage. However, several decades of basic research have challenged this view[5].

In the brain, loss of one set of synaptic inputs spontaneously leads to the formation of new synapses derived from unaffected afferent connections. After forebrain damage, this spontaneous structural and functional plasticity allows the brain to reroute neural information through alternative circuits to regain functions[170]. Similar circuit reorganization spontaneously takes place after incomplete SCI[14,15,17,19]. For example, a lateral hemisection of the spinal cord (Brown–Sequard syndrome) triggers reorganization of intraspinal[14,16,109], brainstem and corticospinal tract[25,26,109] projection circuits that supports remarkable levels of spontaneous recovery, including voluntary skilled movements in humans[20]. Projection neurons spontaneously form detour circuits that relay supraspinal information to spinal circuits below the injury. Such circuit reorganization can reroute task-specific cortical commands to the lumbar execution centers even when all direct descending supraspinal connections are interrupted[13,15,109]. These observations have important implications for spinal cord repair, as they suggest that intraspinal relay neurons, even when newly derived from grafted cells[90], may be sufficient to mediate meaningful recovery.

Another important consideration is the automaticity of neural operations from spinal cord execution centers[95,100]. These circuits have traditionally been referred to as central pattern generators (CPGs) that produce stereotypical motor patterns[100]. This view has advanced over the past decade[171]. It is now recognized that the spinal cord acts as a smart information-processing interface that translates task-specific sensory information and supraspinal inputs into muscle activation patterns that continuously meet behavioral goals and environmental constraints[35,101]. Even after the complete loss of supraspinal inputs, spinal circuits remain capable of using sensory information as a source of control for producing complex motor behaviors, including standing, walking over a range of speeds and directions and even climbing a staircase[31,35,105,172,173]. These results suggest that passing a limited amount of information to the spinal cord below injury may be sufficient to restore meaningful motor control after SCI.

Concepts of spinal cord automaticity, axonal plasticity and circuit reorganization after SCI have established the framework that is steering emerging biological and technological strategies for spinal cord repair and recovery[174].

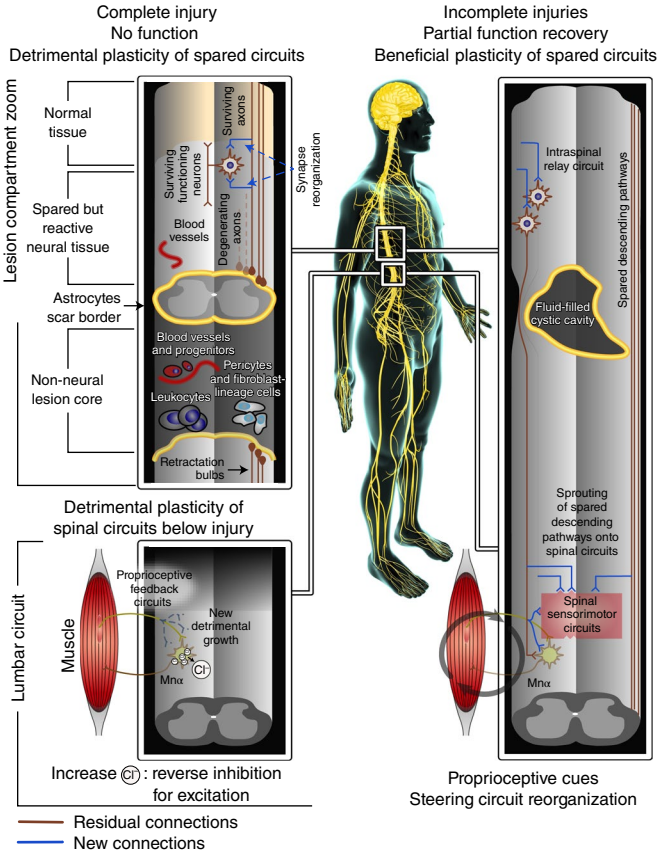


**Fig. 1 | SCI biology and spontaneous recovery mechanisms.** Spinal cord damage can be broadly divided into two categories: complete and incomplete SCI. A complete SCI is obtained experimentally by a full transection of the spinal cord or a complete crush. Anatomically complete SCI is less common in humans. A clinically complete SCI is essentially defined functionally, when no motor and sensory functions can be detected below the SCI, but this can occur in spite of the presence of some spared tissue and connections. After such lesions, detrimental changes continue taking place for decades below the SCI. An incomplete SCI spares tissue bridges containing a variety of ascending and descending pathways, depending on the location of the injury. The anatomical and functional reorganization of these pathways and circuits below the injury support various degrees of functional recovery. Both complete and incomplete SCIs exhibit three distinct lesion compartments: (1) a central non-neural lesion core often referred to as a fibrotic, mesenchymal or connective tissue scar that often contains cystic cavities; (2) a narrow border of reactive astroglia and other cells that intimately surrounds the lesion core; and (3) a surrounding zone of viable neural tissue that is spared and functional but is also reactive and reorganizing. Some of the mechanisms highlighted in this figure have been uncovered in animal models, and it is not yet certain whether human SCI involves similar mechanisms.

found in functioning neural tissue, including hypertrophic reactive astrocytes and microglia that retain their interactions with neurons and synapses undergoing circuit reorganization and remodelling[5,11].

Diverse forms of axonal growth responses have been identified that can occur spontaneously or be induced after SCI. There is a growing consensus that the concepts of 'neural regeneration' and 'axon regeneration' after SCI should be expanded to encompass multiple forms of axonal growth responses that can restore function, ranging from synaptic remodeling in spared and reorganizing neural tissue to axon regrowth across non-neural lesion core tissue[5,11,12] (Fig. 2). Understanding how different cellular and molecular mechanisms regulate different growth responses in different lesion compartments over specific temporal windows is essential to devising mechanism-based approaches to SCI repair.

**Modulating circuit reorganization after incomplete SCI.** The identification of spontaneous circuit reorganization in animal models of SCI has provided valuable insights into repair strategies (see Box 1). After incomplete injuries, intraspinal projection neurons form new 'detour circuits' that relay supraspinal information from above to below the lesion[13–16]. In turn, corticospinal and reticulospinal tract neurons sprout onto these intraspinal relay neurons that connect to regions below the lesion[14–17] (Fig. 1). In general, all descending systems with residual axons that have been studied in animal models exhibit pronounced reorganization after SCI[18]. For example, after lateral hemisection injury in non-human primates, spared corticospinal axons descending in the contralateral white matter extend axon collaterals across the spinal cord midline and sprout into functional spinal cord areas below injury[19,20]. Similar observations

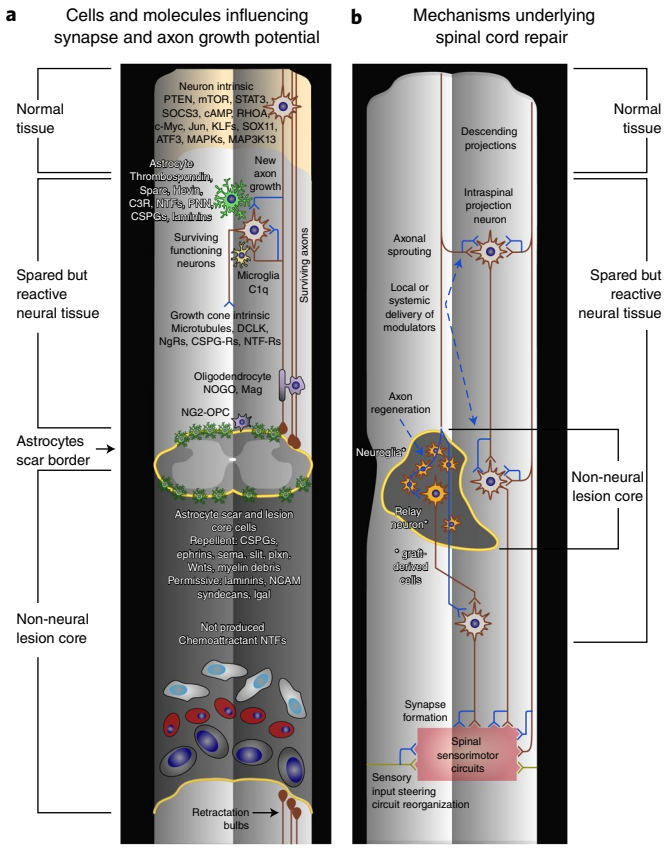


**Fig. 2 | Biological strategies and mechanisms for spinal cord repair.** **a**, Summary of the diverse types of cells and molecules that are known to influence and regulate the potential growth of axons and synapses in the different compartments of a SCI. RHOA, ras homolog family member a; ATF3, activating transcription factor 3; SOX11, Sry-box 11; NTFs, neurotrophic factors; PNN, peri-neuronal net; NgRs, NOGO receptors. **b**, Many mechanisms can be targeted to improve functional recovery, including modulation of axonal sprouting and synapse formation in spared and reorganizing neural tissue, promoting axon regeneration into and beyond non-neural lesion cores, placement of neural-stem-cell-derived grafts providing new relay neurons or neuroglia that supports host axon growth, and modulation of sensory input steering circuit reorganization.

have been described for the reticulospinal, rubrospinal and serotonergic descending systems[17,21,22]. Indirect evidence suggests that similar reorganization and sprouting of descending pathways take place in humans[20,23,24].

Studies in animal models have established causality between sprouting of corticospinal[25,26] and reticulospinal[27] tract neurons and motor recovery. This plasticity within the spinal cord leads to a remapping of motor cortex output to spinal circuits; this pronounced reorganization confers an essential role to the motor cortex in producing movement after injury. Intraspinal projection circuits also play a critical role in mediating recovery[14,15] (Box 1). This dense network of ascending and descending connections within the spinal cord[28] may be a particularly suitable target for SCI repair[29]. Even when multiple incomplete lesions transect all direct descending supraspinal inputs to lumbar execution centers, neurons with intraspinal projections can establish detour circuits that bypass the injuries and relay sufficient information from the brain to restore rudimentary voluntary locomotor functions in rodents[13,15]. In this model, reducing local inhibition within the spinal cord regions embedding these relay pathways augments their ability to mediate locomotor recovery[29]. Similarly, intraspinal relay circuits can mediate voluntary fine finger movements after loss of direct corticospinal tract input to cervical motor centers in nonhuman primates[30]. Together, these observations provide a compelling rationale for conceiving repair strategies that seek either to augment spontaneous relay circuit formation after incomplete SCI, or to restore neural connectivity by bridging axon regrowth across anatomically complete SCI lesions even for short distances into functioning neural tissue, as discussed below.

While SCI deprives spinal circuits from all or some of the supraspinal signals, the spinal cord below the injury continues receiving and interpreting sensory information. Inputs from sensory afferents that remain intact below lesions become an essential source of control in the production of motor behaviors after SCI[31]. Sensory information steers many of the beneficial but also detrimental changes that take place below the lesion. For example, inputs from proprioceptive organs are essential to guide the anatomical and functional reorganization of supraspinal and intraspinal projection neurons that restores locomotion after SCI. Mice with SCI that lack functional proprioceptive circuits display defective rearrangements of descending projection circuits, which abolishes recovery[16]. In turn, the depletion of synapses from descending pathways triggers an aberrant sprouting of sensory afferents onto the available synaptic targets[32,33]. Due to the absence of signals directing this homeostatic plasticity, these changes often lead to degradation of neuronal functions below the SCI, which has been reported in animal models of SCI[32] and in humans[34].

The modification of synapse function and increase of synaptic plasticity represent a promising approach to augment the beneficial effects of rehabilitation and biochemical manipulations. For example, the presence of serotonin, noradrenalin or dopamine agonists augment activity-dependent plasticity during training in various animal models of SCI[35]. In addition, transient exposure of rats to reduced oxygen levels (intermittent hypoxia) activates midbrain raphe serotonergic neurons, the primary source of serotonin to the spinal cord, and triggers brain-derived neurotrophin (BDNF) synthesis in the spinal cord, which together induce serotonin-dependent plasticity of spinal projections[36]. A clinical study has suggested that the combination of rehabilitation and repetitive intermittent hypoxia may improve walking in humans with incomplete SCI[37]. However, confirmation of these results would require a phase 3 clinical trial with a large number of patients.

New advances are also revealing cellular mechanisms of synapse plasticity. For example, the classical complement signals C1q, C3 and C3R have been shown to regulate microglia-modulated synapse pruning[38,39], while molecules such as thrombospondins, glypicans, secreted protein acidic and rich in cysteine (SPARC) and SPARC like 1 (also known as Hevin), produced by astrocytes, are partly responsible for synaptic formation[40–43]. In turn, chondroitin sulfate proteoglycans (CSPGs) and tenascins produced by neurons and astrocytes form perineuronal nets that constrain this synaptic plasticity and associated circuit reorganization[44]. Signaling related to reticulon 4 (RTN4, also known as NOGO) and its receptors also restricts synaptic plasticity via perineuronal net molecules during development and after injury[45]. Accumulating evidence suggests that strategies against CSPGs or RTN4 receptors primarily target perineuronal nets and synaptic plasticity in spared but reactive neural tissue[45–48] rather than axon regeneration across lesions. Axon guidance molecules, such as repulsive Wnt receptors, are also potent inhibitors of axonal growth[49]. In rat models of incomplete SCI, the use of antibodies against these receptors led to a pronounced sprouting from the proximal segments of corticospinal tract axons[26], which augmented functional recovery. More work is needed to identify strategies capable of modulating synapse plasticity and circuit reorganization after SCI.

**Restoring connectivity across complete SCI.** Anatomically complete SCI lesions in humans are dominated by large areas of non-neural lesion core tissue that do not support axon regrowth[11,50,51]

(Fig. 1). Biological approaches to restoring connectivity across such lesions are currently focused on stimulating endogenous axon regrowth through the lesions or grafting new neurons into lesions to re-establish communication through new relay circuits.

Multiple mechanisms regulate axon regrowth after SCI. After development, CNS neurons downregulate their capacity for axon growth. Although spontaneous re-activation of intrinsic growth programs after injury is limited, a steadily growing amount of evidence shows that manipulating neuron-intrinsic signaling through multiple transcriptional regulator pathways in animal models in vivo can stimulate the capacity for axon regrowth of various neuron phenotypes. These pathways notably include phosphatase and tensin homolog (PTEN), mechanistic target of rapamycin (mTOR), signal transducer and activator of transcription 3 (STAT3), suppressor of cytokine signaling 3 (SOCS3), Kruppel-like factors (Klfs), c-Myc, cAMP, mitogen-activated protein kinase kinase kinase 13 (MAP3K13) and others[52–58]. Axon-regrowth capacity can be powerfully activated when tissue around mature neuronal cell bodies is stimulated with inflammatory mediators, such as oncomodulin, zymosan and agonists of toll-like receptor 2 (TLR2) and C-type lectin domain family 7 member A (also known as Dectin-1) receptors[59,60], or by stimulation with growth factors such as insulin-like growth factor 1 (IGF1), osteopontin and ciliary neurotrophic factor (CNTF)[61,62].

Axonal growth in the CNS is also regulated by the presence or absence of chemoattractive or chemorepellent growth factors, or of substrates that support or repel growth. For example, developmental axon growth critically depends on the availability of chemoattractive growth factors such as brain-derived neurotrophin (BDNF) and neurotrophin-3 (NT3)[63–65] and on supportive substrates such as lamining, syndecans and heparan sulfate proteoglycans[65–69]. Although growth-repellent molecules, such as myelin-associated molecules and CSPGs, can influence axon regrowth in vitro and may modulate synapse remodeling after SCI[46–49], there is at present no compelling evidence that they play major roles in regulating axon regrowth across SCI lesions, as discussed in detail elsewhere[5]. The support or repulsion of growing axons by specific molecular cues has been studied in detail in vitro and is determined by relative proportions of attractive and repellent molecules, such that increasing the concentration of one type of cue can overcome the effects of another[70].

Multiple cell types influence axon regrowth in SCI lesions. Activated macrophages cause axon retraction and dieback[71]. Pericytes and fibroblast lineage cells in the non-neural lesion core[6] do not spontaneously support axon regrowth, perhaps because they do not secrete molecules that stimulate axon growth. Consistent with this interpretation, fibroblast cell grafts support robust axon regeneration after SCI only when they produce specific factors that are chemoattractive to axons[72]. 'Scars' formed by astrocytes along lesion borders have long been thought to be the primary cause for axon regeneration failure in the CNS[73,74]. Recent genetic loss-of-function studies in mice challenge this notion. Neither preventing the formation of, nor removing, the astrocyte scar borders in SCI lesions resulted in regrowth of descending motor, ascending sensory or serotonin axons[65]. Furthermore, in both mice and rats, activated and chemoattracted sensory axons regrew robustly despite the presence of astrocyte scar borders[65,75], and preventing or removing these borders reduced stimulated regrowth, suggesting that astrocyte borders can support, rather than prevent, axon growth[65]. Intrinsically activated CNS axons also regenerate robustly despite astrocyte scar border formation in the rodent optic nerve[52,54,59,62]. Axons grow directly along astrocytes during development[76–78] and when appropriately stimulated after CNS damage in adult mammals[65,75,79] and lower vertebrates[80]. These combined findings provide strong evidence that astrocyte scar borders are not a primary cause for the failure of axons to regrow across SCI lesions and that strategies other than simply manipulating these borders will be needed to achieve this type of regrowth.

Given the multiple time-dependent mechanisms that influence axon regrowth across lesions, rational strategies for therapy after SCI will likely require simultaneous targeting of multiple mechanisms with distinct temporal windows. There is substantial evidence indicating that using a combination of multiple therapeutic strategies increases axon growth. For example, the activation of sensory neurons in animal models of SCI has long been recognized to increase growth into permissive cell grafts or across lesions[63,81,82]. Notably, activated neurons do not grow well through non-neural lesion cores but do grow well along supportive cues present in spared neural tissue[62,79,83]. Recent gain- and loss-of-function studies in mouse and rat models of anatomically complete SCI showed that neuronal activation, substrate support and chemoattraction were each required for recovery, but only together were these strategies sufficient to produce robust regrowth of sensory axons[65] and propriospinal axons[75] through non-neural lesion cores. Findings from these two neuronal systems suggest that achieving robust regrowth of endogenous axons across lesion cores will likely have three requirements: (1) activating intrinsic neuronal growth programs, (2) availability of axon-supportive growth substrate and (3) providing growth factors that are chemoattractive to axons[75]. It is important to note that the necessary axon-chemoattractive factors were different for each of the two neural systems studied, sensory and propriospinal neurons, indicating that more work will be needed to identify specific molecular targets that are able to stimulate and attract the growth of axons from the heterogeneous populations of brain, brainstem and intraspinal projection neurons that may be of functional interest after SCI.

In various animal models, cell grafts that repopulate non-neural cores with growth-supportive neuroglia, such as Schwann cells[84,85] or astroglia[86,87], facilitate the growth of host axons across non-neural lesion cores and improve the functionality of residual fibers[88]. Clinical trials are evaluating the safety and efficacy of autologous Schwann cell grafts for SCI[89]. Another approach to promote the formation of relay circuits consists of grafting sources of new intraspinal neurons. In the presence of growth factors and supporting matrices, caudalized neural progenitor grafts not only survive in the hostile non-neural environment, but also differentiate into a variety of neurons and glia that repopulate the lesion core and send extensive axonal projections into host tissue both caudal and rostral to the injury in rodents[90]. The cell adhesion molecule neuronal growth regulator 1 (NEGR1) is one of the factors enabling permissive axon–myelin interactions, which allows myelin to stimulate axonal outgrowth from the grafted cells. Moreover, the grafted neurons release various growth factors[91] that attract an impressive number of synapses from all of the host's systems that innervate the spinal cord, including robust regeneration of the recalcitrant corticospinal tract[92]. Neural progenitor grafts form de novo relay circuits that restored a partial communication across anatomically complete SCI[64,90,92,93]. Interestingly, host axons exhibit functionally appropriate preferences when forming contacts with grafted neurons. Despite this striking reconstitution of spinal cord tissues observed in rodents[90] and nonhuman primates[94], however, functional recovery has remained limited. These results thus provide important proof-of-concept information, but additional studies are necessary to understand how to guide, control and functionally integrate the grafted neurons into the host motor-circuit communication matrix[95] to restore meaningful function.

**Biomaterials to improve biological repair.** Biomaterials hold considerable promise in augmentation of SCI repair. For example, injectable and resorbable polypeptide hydrogels can provide temporary depots for the prolonged release of growth factors that chemoattract regrowing axons[65,75]. Such depots, when temporally and sequentially placed, can chemoattract axons to regrow across complete SCI lesions and into spared neural tissue to contact neurons[75]. Hydrogel–collagen networks can be engineered to provide

oriented scaffolds that facilitate the alignment of grafted cells and thereby direct axon regrowth[96]. Bioengineered scaffolds with linear guidance channels might prevent regenerating axons from developing tortuous trajectories[12], instead directing their outgrowth along linear paths across the lesion site[97]. Survival and differentiation of grafted cells can be enhanced and directed by biomaterial vehicles that provide substrate and growth factors[90]. Biomaterial approaches to CNS repair are slowly but steadily advancing[98,99].

## Technological approaches

Major advances, but also failures, in the fields of neurosurgery, robotics, computational neuroscience and neuroengineering have populated SCI medicine with a flurry of wearable and implantable neurotechnologies to enable and augment function. These treatments have historically been divided into restoration therapies, replacement strategies and rehabilitation procedures. However, the marriage of these engineering strategies is occurring at such a rapid pace that these categories are progressively becoming obsolete, if not misleading. Indeed, all current promising strategies share a common theme: capitalize on the intrinsic capacity of spared circuits to produce movement, and on the remarkable ability of these circuits to reorganize with training to augment recovery. Early achievements of these bourgeoning neuroprosthetic treatments are providing a glimpse at the therapeutic potential of technological approaches after SCI.

**Engineering strategies to enable motor control.** Sensorimotor circuits embedded in the spinal cord can translate task-specific sensory feedback into organized patterns of muscle activity underlying a broad repertoire of motor behaviors[31,100,101] (Box 1). These circuits are often intact after SCI but lack the supraspinal sources of modulation and excitation essential for enabling their functionality. This understanding has triggered the development of various neuromodulation therapies that seek to compensate for these missing supraspinal inputs to reactivate spinal circuits. For example, in rats with partial SCI, deep brain stimulation of the midbrain locomotor region can engage reticulospinal neurons that retain connections across the injury. The resulting descending drive leads to the activation of spinal circuits, which improves paretic locomotion[102]. However, this neurosurgical intervention is contingent on synaptic inputs from reticulospinal neurons, which limits the spectrum of SCI severities that might be addressed with this approach. Moreover, the relevance of this ancestral brainstem locomotor system for volitional walking activities remains unclear in humans.

To address more severe injuries, both pharmacological and electrical neuromodulation therapies have been delivered directly to spinal cord regions containing sensorimotor circuits involved in movement production (Fig. 3). Monoaminergic medications[31,103,104] and electrical stimulation protocols applied transcutaneously[104], epidurally[105–112], subdurally[113] and intraspinally[114–116] have enabled unexpected levels of leg and hand motor control in animal models and humans with paralysis[106,116–118]. Electrical stimulation protocols may also improve cardiovascular and respiratory functions[119,120]. The underlying mechanisms remain debated[121,122], but evidence suggests that these electrical stimulations converge on a common target. Indeed, dorsally applied electrical fields spread toward dorsal roots, where sensory afferents reside[123]. Due to their lower resistance to electrical currents, large-diameter proprioceptive fibers are the first neural structures recruited by the stimulation[121]. Intraspinal stimulation likely relies on the same mechanisms[124]. If similar outcomes are confirmed, this technology, which requires arrays of electrodes penetrating the spinal cord gray matter, would become less attractive than other strategies.

Due to their broad integration within sensorimotor networks, recruitment of proprioceptive afferents increases excitability of spinal circuits, which augments their responsiveness to task-specific

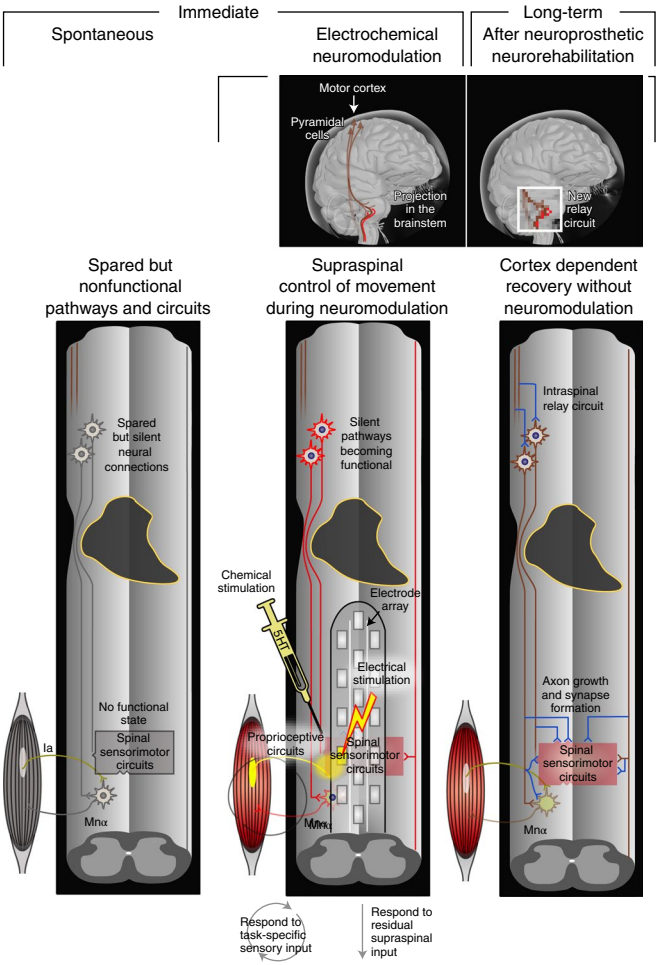


**Fig. 3 | Engineering strategies to enable immediate and long-term recovery of motor functions.** After a severe but incomplete SCI, the sensorimotor circuits producing motor activity are spared, but they lack the essential source of modulation and excitation to be functional. Descending pathways are partly spared but fail to activate these circuits in order to mediate muscle contractions. The delivery of chemical and/or electrical neuromodulation therapies to the lumbar or cervical spinal cord below the injury immediately enables spinal sensorimotor circuits to respond to task-specific sensory input and residual supraspinal input in order to produce functional movements. In conjunction with neurorehabilitation, this intervention promotes an extensive reorganization of spared circuits and residual connections in the brainstem and spinal cord that mediates functional recovery. After training, motor control occurs without the need of the electrochemical neuromodulation therapies.

sensory information and residual signals from the brain. During spinal cord stimulation, individuals with motor complete paralysis regained the ability to activate paralyzed muscles and initiate isolated movements of the leg[106,117,125]. In rats with severe contusions, pharmacological and electrical neuromodulation therapies applied to the lumbar spinal cord instantly enable the motor cortex to trigger and modulate robust locomotor movements of paralyzed legs[27]. Because these injuries abolish all corticospinal tract projections, the cortical command is transferred downstream through glutamatergic projections originating from the ventral gigantocellular reticular nucleus. Due to their distributed topology in the white matter, these pathways systematically survive the injury, regardless of the inherently variable location of damage. The anatomy and function of reticulospinal pathways are well-conserved across mammals[126], and reticulospinal systems likely contribute to improving recovery from

SCI in humans[24]. These results suggest that clinically complete injuries often spare descending projections, in particular reticulospinal pathways, but these residual neural connections are insufficient to voluntarily elicit detectable muscle contractions[106,117,127,128].

These clinical research results have triggered a surge of interest in the development of spinal cord stimulation technologies[105,129]. These new strategies aim to activate the proprioceptive fibers in the posterior roots[122,123]. Consequently, targeting proprioceptive fibers located in a given lumbosacral posterior root using a spatially selective electrode configuration provides preferential access to the premotor neurons and motoneurons[130,131] embedded in the segment innervated by this root[122,123]. This translates into closed-loop stimulation protocols whereby short bursts of spatially selective electrical stimulation are delivered with a timing that coincides with natural activation of motoneurons[132]. These spatiotemporal neuromodulation therapies enable a refined control over the movements of paralyzed legs in animal models and humans[105,129]. For example, if the algorithms that control this neuromodulation are adjusted on the basis of real-time movement feedback, this enables rats with complete SCI to climb staircases of various heights and lengths with precision and fluidity[133]. Residual supraspinal inputs can also modify the impact of the electrical stimulation on the spinal cord executive centers, both positively and negatively, in order to modulate the movements voluntarily[27,109,111,117].

Compared to continuous stimulation, spatiotemporal stimulation increases the amplitude and robustness of leg movements, which enabled the sustained production of full weight-bearing locomotion in animal models and humans[105,129,133]. These spatiotemporal stimulation protocols enabled graded control over the activity of otherwise paralyzed muscles during walking, thus providing the opportunity to engage activity-dependent mechanisms during rehabilitation, as discussed below.

**Engineering strategies to bypass lesions.** A brain–computer interfaces (BCI) decodes motor or cognitive intentions from a neural sensing interface and translates these predictions into executive commands for actuators. Historically, BCI treatments have focused on connecting people who have lost the ability to speak or move with assistive devices. These neurotechnologies allow people with paralysis to type words at a fast pace[134,135] and to operate multi-articulated prosthetic arms to execute activities of daily living using neural signals recorded directly from the brain[136,137].

BCI research is now undergoing a rapid transition from substitution to restoration therapies. The new waves of BCIs aim at re-establishing bidirectional communication between the brain and denervated body parts[129,138–142] (Fig. 4). For example, cortical signals have been directly linked to neuromuscular stimulation protocols to reanimate paralyzed muscles. These neural bypasses enabled functional upper limb movements in two persons with tetraplegia[138,139]. Conversely, encoding touch pressure information into somatosensory cortex stimulation protocols allowed a paralyzed person to recognize pressure-like sensations in individual fingers of a robotic hand[142]. Leg motor cortex activity has been interfaced wirelessly to spinal cord stimulation protocols to establish a brain–spine interface that restores natural locomotor movements of paralyzed limbs in rodent[143] and non-human primate[129] models of SCI. Similar approaches may improve upper limb functions[115,118], but the more sophisticated control of manual dexterity and the permanent gray matter damage associated with cervical injuries add significant challenges. However, contrary to the high threshold required to attain useful locomotor function recovery, even relatively modest improvements in hand function can translate into a meaningful increase in quality of life[3].

The translation of these breakthroughs into common medical treatments for people with paralysis is facing a series of practical, financial and technological roadblocks[144]. Practically, the functional

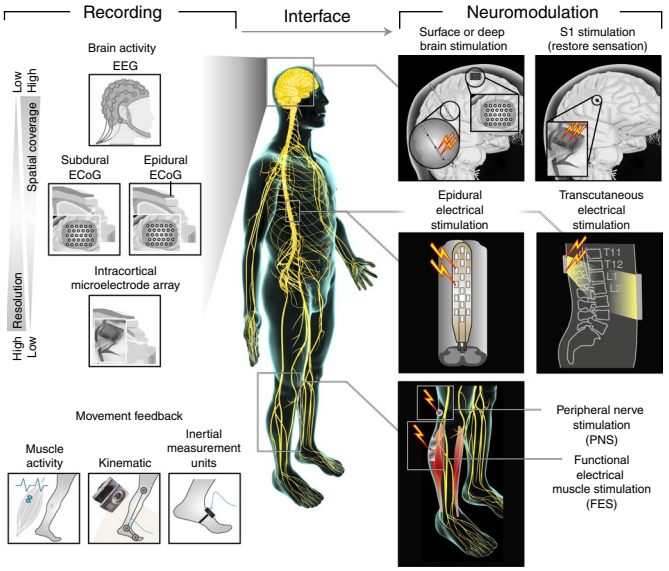


**Fig. 4 | Engineering technologies to interface motor intentions with denervated body parts.** Current brain recording technologies impose a trade-off between resolution, spatial coverage and invasiveness. Motor intentions or motor states decoded from neural recordings or movement feedback signals can be interfaced to neuromodulation therapies or stimulation protocols to enable or induce movements and sensations. EEG, electroencephalogram; ECoG, electrocorticogram.

benefit of BCI devices remains relatively modest in comparison with their manifold technical challenges and financial burdens for society[144]. Advanced BCI treatments employ Utah arrays that are inserted into the cerebral cortex to record neural activity. Conceived in the 1990s, this grid of silicone-based electrodes is the only intracortical neural probe approved for clinical use. However, the quality of neural signals extinguishes rapidly. Cortical grids placed epidurally or subdurally allow more stable neural recordings (Fig. 4), but their spatial resolution may be insufficient for advanced prosthetic control[144]. Moreover, daily use of these neural prostheses will only be possible with the support of wireless recording technologies and brain-decoding algorithms that do not require constant recalibration. Likewise, current technologies to modulate the human CNS do not meet the requirements of prosthetic applications[145]. Advanced therapies rely on implantable stimulation technologies endowed with real-time wireless communication, and on next-generation interfaces targeting specific neural structures with electrical, chemical and even optical stimulation modalities. Multiple academic institutions, foundations and companies are addressing these challenges.

**Engineering rehabilitation to augment recovery.** Activity-based therapies are common in medical practice for enhancing recovery from SCI. The underlying molecular mechanisms remain unclear, but it is now accepted that the repeated activation of the sensorimotor system augments activity-dependent plasticity of spared circuits and residual neural connections, which leads to functional improvements[18,35,146,147]. Consequently, a large number of neurotechnologies have been developed to augment activity, and thus plasticity, after SCI. For example, motor cortex electrical stimulation promotes activity-dependent sprouting of spared corticospinal tract axons, which improved skilled locomotion in rodent models of partial SCI[148,149]. Despite conflicting results, transcranial magnetic stimulation applied over both the leg and arm regions of the human motor cortex also enhance the transmission along residual neural pathways, which has improved motor functions and reduced spasticity

in paraplegic and tetraplegic patients[150,151]. Similarly, paired associative stimulation of neural structures above and below SCI promote lasting augmentation of cortical and spinal circuit outputs, both in animal models and humans with SCI[152,153]. Electrical stimulation of the spinal cord by single corticospinal tract neurons also triggers a durable modification of neural connectivity[154–156]. This activity-dependent stimulation increases the strength of terminal projections from single neurons through spike-timing-dependent plasticity[157]. These approaches may increase recovery after partial injuries that spare corticospinal tract projections, which is a key predictor of spontaneous recovery after acute SCI[158]. For this reason, various groups are evaluating whether long-term use of the neural bypasses described above during rehabilitation may augment plasticity and recovery[143,159].

Experiments in animal models of SCI illustrate that the extent of activity-based plasticity correlates with the volume and intensity of that activity[147]. Due to the depressed excitability of spinal circuits, the severely injured spinal cord does not respond robustly to task-specific sensory information, thus limiting the benefit of activity-based therapies[147,160]. However, neuromodulation therapies restore the ability of motor execution centers located in the spinal cord to process sensory information to produce movement[111,112,117,156], which provides the possibility to train with high levels of activity. Encouraging contribution of supraspinal centers is essential to restore volitional motor control. Step training on a treadmill, which does not require supraspinal contribution in animal models[31], mediates robust activity-dependent plasticity of spinal circuits[31,35] but fails to restore functional interactions with supraspinal centers[109]. Instead, rehabilitation in a robotic body weight support system that favors these interactions restores volitional motor functions. After injuries leading to permanent leg paralysis, both rats and humans trained with such robotic support and neuromodulation therapies regained the ability to transform contextual cues into task-specific motor commands to walk over ground over a range of speeds or adjust their step height as needed to climb a staircase[27,109,111]. However, volitional movements also returned without neuromodulation, both in animal models[27] and humans[111,161]. Unbiased anatomical experiments of whole-brain and spinal cord in animal models showed that this recovery relies on an extensive and ubiquitous plasticity of residual connections whereby the cortical command is rerouted to lumbar circuits through de novo brainstem pathways[27] and/or intraspinal relays[109]. The mechanisms responsible for this activity-dependent plasticity remain enigmatic. Neural activity triggers growth factor synthesis[162], calcium-dependent myelin sheath formation[163], chloride homeostasis regulation[164], synaptic plasticity and many other molecular mechanisms that most likely contribute to neural repair.

Accumulating evidence suggests that the interplay between top-down supraspinal signals and bottom-up proprioceptive information plays a critical role in mediating this recovery. The absence of proprioceptive information prevents descending pathway reorganization after injury[16]. In turn, electrical stimulation enables motor control through the activation of proprioceptive pathways[122,123]. Many descending systems that are engaged during rehabilitation converge on these circuits[27,109]. This conceptual framework is steering the development of new engineering strategies that forcefully link top-down and bottom-up signaling pathways during rehabilitation. For example, paraplegic individuals were trained in an exoskeleton that was actuated based on non-invasive brain recordings[165]. Artificial sensory feedbacks were delivered to both arms in order to feed proprioceptive information from both legs to the spinal cord above the injury. Over time, this closed-loop system restored sensation in some of the originally denervated dermatomes. Likewise, brain-controlled stimulation of the spinal cord below the injury augmented the beneficial impact of rehabilitation on the recovery of locomotion in rats with severe SCI[143]. These rehabilitation programs closing the loop between circuits located above and below the injury may further increase use-dependent plasticity of residual connections[155,159], but more work is needed to uncover the underlying mechanisms.

While various engineering approaches have yielded impressive outcomes in laboratory environments, it is important to realize that patients still favor wheelchairs over other alternatives to ambulate[166]. For example, various insurances reimburse the purchase of lower limb exoskeletons to patients with SCI. However, current technologies involve high energy requirements, unpractical setting procedures and complex operations to ambulate at relatively low speed compared to wheelchairs. These limitations emphasize the need to refine current technologies. For example, implanted devices that can be operated with a voice controller open practical perspectives for use in daily life. These technologies also offer the opportunity to continue effective rehabilitative training at home or in specialized gyms in order to take advantage of the continuing potential for plasticity that expands beyond the transient rehabilitation programs currently delivered to individuals with SCI.

## Future directions

Current biological and engineering strategies have shown therapeutic potential in animal models, but their ability to mediate clinically important improvements after severe SCI remains elusive. Since these treatments target distinct mechanisms, their combinations are expected to be synergistic. While logical, merging fundamentally different approaches has turned out to be more complex than originally thought. For example, activity-based therapy in the presence of plasticity-enhancing strategies uncovered complex interactions between both interventions[47,167–169]. These studies revealed that the specific relationships between the practiced exercises and the temporal windows for delivering each therapy determined the balance between beneficial and detrimental plasticity. Moreover, many failed combinatorial attempts still linger in laboratory notebooks. Despite these unexpected outcomes, dubious combinations of unproven cell treatments, immature engineering strategies and intense exercise programs have unfortunately flourished in clinics offering medical tourism.

Thus far, combinatorial attempts were designed algebraically, expecting simply additive results without considering the interactions between their respective mechanisms. Based on the knowledge summarized in this review, various combinatorial strategies could be envisaged that activate intrinsic neuronal growth programs, establish a permissive growth environment, deliver chemotropic gradients to encourage axonal regeneration into and beyond the environment, graft neural stem cells that form new relay circuits and deploy engineering solutions that foster the integration of regenerating axons and de novo relay circuits into CNS operations through rehabilitation. However, this vision may be simplistic and deceptively incremental.

With appropriately targeted approaches, however, biological and engineering strategies may interact to catalyze each other. For example, biological interventions that modulate axonal growth, lesion environments and even learning and memory may increase the anatomical and functional reorganization of the circuits that underlies the recovery of voluntary motor functions in response to neuroprosthetic rehabilitation. In turn, engineering strategies involving brain-controlled modulation[129,143] of genetically targeted neurons[29] may critically engage neurons with regrowing axons and thus facilitate the integration of newly formed connections, which have been stimulated to regrow by biological interventions, into the operations of the CNS.

The SCI research community must reflect on exploiting engineering solutions to target mechanisms that will amplify biological repair treatments, and inversely, envision mechanism-based biological strategies able to augment the effects of technological interventions. These combinatorial therapies will need to obey strict

**Box 2 | Relevant animal models of SCI**

Effective therapeutic developments require selecting experimental models that are appropriate for evaluating the impact of the tested intervention on the targeted repair mechanisms and are still relevant for clinical perspectives. The majority of current interventions are conducted in rodent models that undergo a partial cut of the spinal cord. These precise injuries are useful to decipher the mechanisms of recovery since the interrupted tracts are well characterized. Moreover, they lead to spontaneous functional recovery, which allows monitoring therapy-mediated improvements. However, this type of lesion fails to reproduce many of the features that characterize the majority of spinal cord damage in humans. After partial cut injuries, humans exhibit extensive spontaneous functional recovery.

Instead, severe contusion or crush SCI in rodent models presents all the key hallmarks of the more frequently observed injuries in humans, including permanent paralysis. Moreover, recovery from contusion SCI appears to rely on mechanisms that are distinct from those involved in movement restoration after cut injuries[27]. Due to variable outcomes and severity of deficits, however, contusion injuries are not always used in animal models for preclinical tests of potential interventions. We believe that spinal cord repair interventions should therefore be tested in both cut and contusion or crush models, with severities that are relevant clinically.

Another key consideration is the importance of nonhuman primate models of SCI. The technical difficulties, complex logistics, exuberant costs and intimidating ethical issues are refraining translational scientists from testing and optimizing their therapies in this model. However, we argue that there is much to gain in solidifying preclinical results in primate models, and adapting procedures and technologies to the size and specificities of primate species. Considering the staggering cost of clinical trials, we feel that a tremendous amount of information may derive from small, well-structured studies in nonhuman primate models of SCI before contemplating applications in humans.

temporal windows. This translational strategy requires a careful selection of rodent SCI models and, in many instances, a necessary work in nonhuman primate models (Box 2).

We thus advocate tailoring combinations of biological and engineering strategies derived from the identified interactions between their respective mechanisms over the course of recovery from SCI. Only through these combinatorial, time-dependent interventions will we appropriately target multiple facets of spinal cord repair and mediate clinically meaningful functional improvements. These concepts may apply to other CNS disorders. While there are challenges ahead, only through this partnership between biologists and engineers will treatments be conceived to advance and maybe win the fight against paralysis.

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## Competing interests

G.C. holds various patents in relation to the reviewed work, and is a founder and shareholder of GTX medical, a company developing a therapy for spinal cord injury.

## Additional information

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