UNIVERSITÀ DEGLI STUDI DI GENOVA

Scuola di Scienze Mediche e Farmaceutiche

CORSO DI LAUREA IN MEDICINA E CHIRURGIA

Evaluation of Spinal Cord Stimulation for Motor Recovery in Patients with Paraplegia Following Spinal Cord Injury: Preliminary Results from a Pilot Study

Relatore:
Prof. Marco Bove
Correlatori:
Dott. Luigi Albano
Prof. Pietro Mortini

Candidato:
Angelo Comerci
Matricola: 5087929

Anno accademico 2025-2026

Table of Contents

Abstract (English)

Background: Spinal cord injury (SCI) is a major cause of neurological disability, resulting in motor, sensory, and autonomic impairment below the level of injury. Recent evidence suggests that epidural spinal cord stimulation (SCS), combined with rehabilitation, may promote motor recovery by modulating residual spinal circuits. This study evaluated the effects of SCS in patients with chronic thoracic SCI.

Methods: Ten patients with chronic traumatic thoracic SCI (AIS A–C) underwent implantation of a 32-contact epidural paddle electrode followed by individualized stimulation protocols and intensive rehabilitation within a prospective clinical trial (NCT05926843). Motor and functional outcomes were assessed at baseline, 3 months, and 6 months using muscle strength (MRC scale and dynamometry), single joint movements, standing ability, overground walking (10MWT and 6MWT), and spasticity (Modified Ashworth Scale, MAS).

Results: Motor-incomplete patients showed progressive improvements in lower-limb strength, standing, and walking, with partial recovery maintained even without stimulation after rehabilitation. In motor-complete patients, voluntary movement remained stimulation-dependent, although SCS consistently elicited reproducible muscle activation, enabling assisted standing and overground walking. Walking performance improved significantly over time, while spasticity was abolished during active stimulation and remained reduced at follow-up.

Conclusions: Epidural SCS combined with intensive rehabilitation is a feasible and promising therapeutic strategy for chronic SCI, improving locomotor function and reducing spasticity. These preliminary findings support further controlled studies to optimize stimulation paradigms and identify predictors of functional recovery.

Abstract (Italian)

Background: Le lesioni midollari rappresentano una delle principali cause di disabilità neurologica, determinando deficit motori, sensitivi e autonomici al di sotto del livello della lesione. Evidenze recenti suggeriscono che la stimolazione epidurale del midollo spinale (SCS), associata alla riabilitazione, possa favorire il recupero motorio attraverso la modulazione dei circuiti spinali residui. Il presente studio ha valutato gli effetti della SCS in pazienti con lesione midollare toracica cronica.

Materiali e Metodi: Dieci pazienti con paraplegia cronica da lesione midollare traumatica toracica (AIS A–C) sono stati sottoposti all'impianto di un paddle epidurale a 32 contatti, seguito da protocolli di stimolazione personalizzati e riabilitazione intensiva nell'ambito di uno studio clinico prospettico (NCT05926843). Gli outcome motori e funzionali sono stati valutati al basale, a 3 e 6 mesi mediante forza muscolare (scala MRC e dinamometria), movimenti articolari, stazione eretta, deambulazione overground (10MWT e 6MWT) e spasticità.

Risultati: I pazienti con lesione motoria incompleta hanno mostrato un progressivo miglioramento della forza, della stazione eretta e della deambulazione, parzialmente mantenuto anche in assenza di stimolazione dopo la riabilitazione. Nei pazienti con lesione motoria completa, il movimento volontario è rimasto dipendente dalla stimolazione, che ha tuttavia consentito un'attivazione muscolare riproducibile, la stazione eretta assistita e la deambulazione. La spasticità è risultata abolita durante la stimolazione e ridotta al follow-up.

Conclusioni: La SCS associata a riabilitazione intensiva rappresenta una strategia terapeutica promettente per il trattamento delle lesioni midollari croniche, migliorando la funzione motoria e riducendo la spasticità. Questi risultati preliminari supportano studi controllati su casistiche più ampie per ottimizzare i protocolli di stimolazione e identificare i predittori del recupero funzionale.

List of abbreviations

10MWT	10-MeterS Walking Test
6MWT	6-Minutes Walking Test
AD	Autonomic Dysreflexia
AL	Adductor Longus
ALS	Antero-Lateral System
AMES	Assisted Movement with Enhanced Sensations
BCI	Brain Computer Interface
BF	Biceps Femoris
BSCB	Blood Spinal Cord Barrier
BWSTT	Body Weight Support on Treadmill Training
C	Cervical
CGP	Central Pattern Generator
CNS	Central Nervous System
DAP	Deep Anal Pressure
DAS	Descending Antinociceptive System
DBS	Deep Brain Stimulation
DCML	Dorsal Column Medial Lemniscus
DREZ	Dorsal Root Entry Zone
ECM	Extracellular Matrix
EMG	Electromyography
ENS	Enteric Nervous System
FES	Functional Electrical Stimulation
FRA	Flexor Reflex Afferents
GLmax	Gluteus Maximus
GLmed	Gluteus Medius
GM	Gastrocnemius Medialis
HF-SCS	High-Frequencies Spinal Cord Stimulation
HRV	Heart Rate Variability
IASP	International Association for the Study of Pain
IL	Iliopsoas
IPG	Implantable Pulse Generator
ISAFSCI	International Standards for Autonomic Function after Spinal Cord Injury
ISNCSCI	International Standards for Neurological Classification of Spinal Cord Injury

L	Lumbar
LC	Locus Coeruleus
LEP	Laser Evoked Potential
LF-SCS	Low- Frequencies Spinal Cord Stimulation
LMN	Lower Motor Neuron
LT	Light Touch
MAP	Mean Arterial Pressure
MAS	Modified Ashworth Scale
MEP	Motor Evoked Potential
MRC	Medical Research Council
MU	Motor Units
MUNE	Motor Unit Number Estimation
NO	Nitric Oxide
NP	Neuropathic Pain
OH	Orthostatic Hypotension
PAD	Primary Afferent Depolarization
PAG	Periaqueductal Gray
PEG	Polyethylene-Glycol
PNS	Parasympathetic Nervous System
PP	Pinprick
PSFS	Penn Spasm Frequency Scale
QST	Quantitative Sensory Testing
RAGT	Robotic Assisted Gait Training
RF	Rectus Femoris
ROM	Range of Motion
RVM	Rostral-Ventromedial
S	Sacral
SC	Spinal Cord
SCI	Spinal Cord Injury
SCS	Spinal Cord Stimulation
sEMG	surface Electromyography
SEP	Somatosensory Evoked Potential
SM	Semimembranosus
SNS	Sympathetic Nervous System
T	Thoracic

TA	Tibialis Anterior
TENS	Transcutaneous Electrical Nerve Stimulation
TUGT	Timed Up and Go Test
UMN	Upper Motor Neuron
VAC	Voluntary Anal Contraction
VL	Vastus Lateralis
VPL	Ventral Postero-Lateral
WISCI	Walking Index for Spinal Cord Injury
ZPP	Zone of Partial Preservation

1. Introduction

1.1 Spinal cord organization

1.1.1 Spinal cord anatomy

The spinal cord (SC) is a pivotal structure of nervous system as it is a vital link between the brain and the body, and vice-versa. The SC represents the caudal continuation of the *medulla oblongata*, and it runs within the vertebral canal, terminating at the level of the *conus medullaris*, which in adults is commonly located around L1 vertebral body. The SC is approximately 40 to 50 cm long (shorter than the vertebral column, resulting from the differential growth rates of the neural and vertebral structure during embryonic development) and 1 cm to 1.5 cm in diameter. Two consecutive rows of nerve roots emerge on each of its sides: these nerve roots join distally to form 31 pairs of spinal nerves, which are divided into: 8 cervical, 12 thoracic, 5 lumbar, 5 sacral, and 1 coccygeal nerve. In the cervical region, spinal nerves C1–C7 exit above their corresponding vertebrae, whereas from C8 downward they exit below. The cervical roots have a horizontal trajectory; the thoracic roots descend obliquely, while the lumbosacral roots run vertically forming the *cauda equina*. The SC is a cylindrical structure of nervous tissue antero-posterior flattened, and it is composed by four regions: cervical (C), thoracic (T), lumbar (L) and sacral (S).

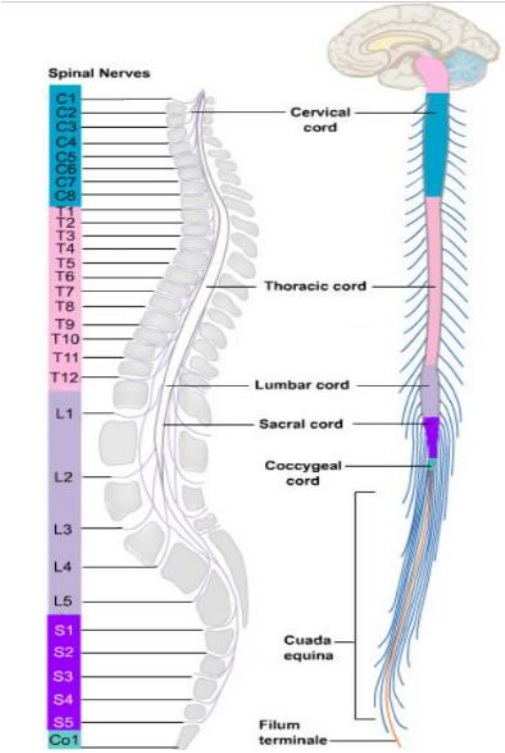


Figure 1: Organization of SC.
Source: https://nba.uth.tmc.edu/neuroscience/

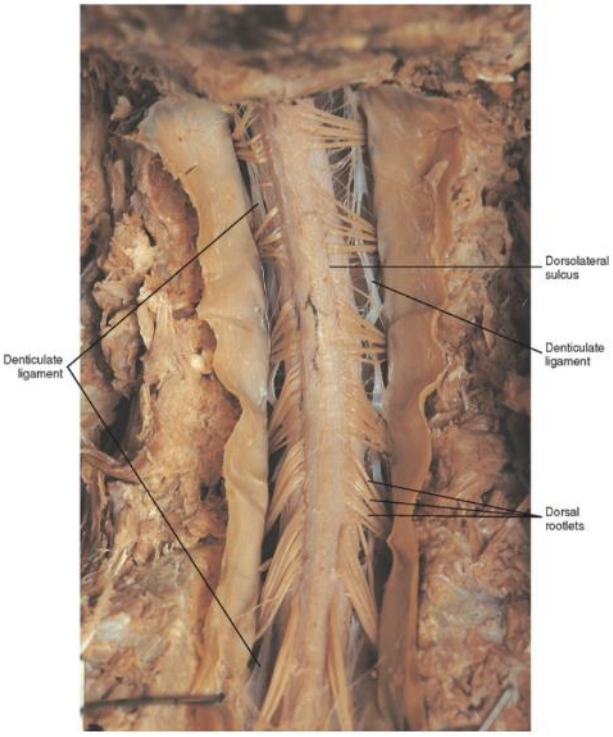


Figure 2: Dorsal view of SC within the vertebral canal (from a cadaveric specimen). The dura has been reflected laterally with pins.
Source: https://basicmedicalkey.com/

Two enlargements can be identified along its length, namely the cervical enlargement (C4-T2) and the lumbosacral enlargement (L1-S2). The last two structures reflect the higher density of neurons due to the limb's innervation (1).

The SC is sheathed in the same three meninges as is the brain:

- ***Dura mater*:** is the stiff outer sheath; the SC is anchored to the *dura* by a series of lateral denticulate ligaments deriving from the *pia* folds that protect the SC from stretching.
- ***Arachnoid mater*:** lies beneath the *dura mater* and it is loosely adherent to the *dura* defining the *subarachnoid* space.
- ***Pia mater*:** adheres closely to the SC surface and gives rise to the denticulate ligaments.

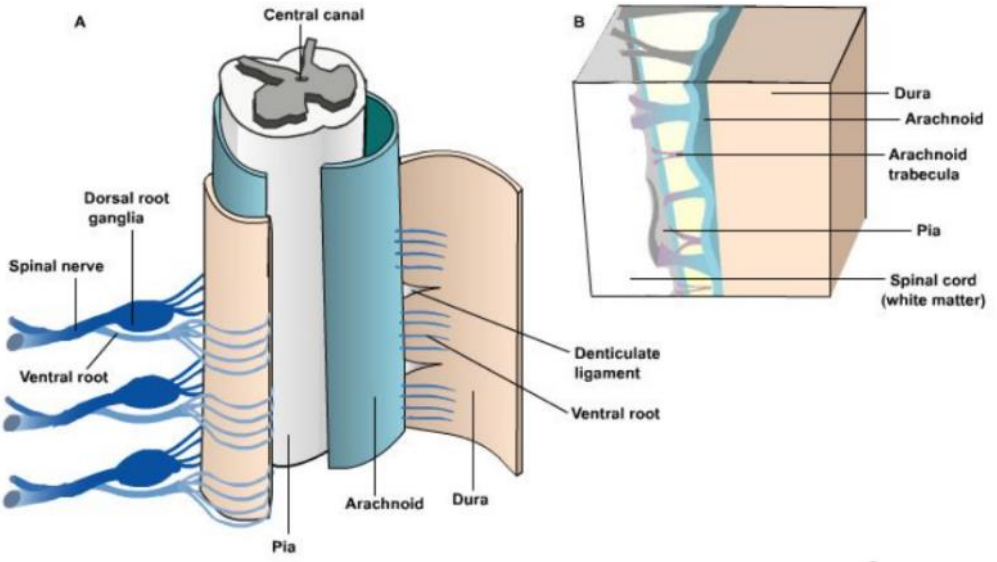


Figure 3: ***(A)****The three meninges, the denticulate ligaments and the dorsal root ganglion.* ***(B)*** *An enlarged drawing of the meninges.*
Source: https://nba.uth.tmc.edu/neuroscience/

The SC contains longitudinal columns of nuclei (gray matter) enclosed by the ascending and the descending tracts (white matter) and in the center there is a tiny canal filled with cerebrospinal fluid (CSF). This canal is surrounded by a single layer of cells: the ependymal layer. The gray matter is a region containing cell bodies and has a H or butterfly shape. The anterior and posterior commissures encase the central canal.

1.1.2 Spinal gray matter organization: columns and Rexed *laminae*

The architecture of the spinal gray matter is better understood through two complementary organizational principles: the longitudinal nuclear columns and the transverse laminae. The columnar organization, recognized by early neuroanatomists (such as Cajal, Clarke and Sherrington) reflects the arrangement of functionally homogeneous neuronal groups that extend vertically across multiple segments. These columns (motor, autonomic and sensory) mirror the

segmental distribution of musculature and visceral systems, and they provide the structural basis for the somatotopic and autonomic maps that govern spinal function (2). The gray matter is divided primarily into anterior and posterior horns; in addition, at the level of T1-L2 there is the lateral horn. The anterior horn gives rise to the anterior nerve root (which carries motor information), whereas the posterior horn gives rise to the posterior nerve root (which carries sensory information). Lastly, the intermediate horn carries autonomic function through the sympathetic and parasympathetic systems. In the early 1950s, Rexed divided the gray matter in the SC of the cat initially into 9 layers; later the division was extended to the humans. Afterward, the gray commissure was labelled as lamina 10 (3,4).

Dorsal horn (laminae 1-6)

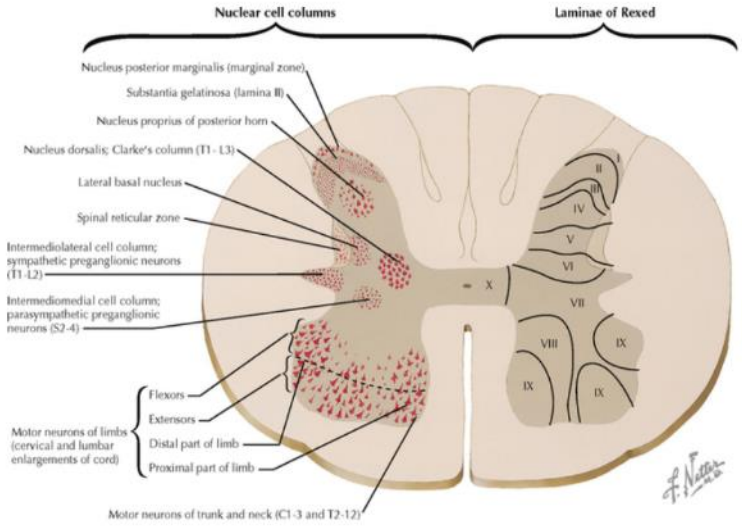


Figure 4: Gray matter organisation of the SC.
Source: Jones HR, Burns E, Aminoff MJ, Pomeroy S (2013)
The Netter Collection of Medical Illustrations: Nervous System, Vol. 7, Pt. 2, Spinal Cord and Peripheral Motor and Sensory Systems, pp. 49–78.

The dorsal horn is the primary site of somatosensory integration. It contains the *laminae* 1-6 and it represents the primary site of somatosensory integration. The dorsal horn can be divided into three portions:

- **Superficial dorsal horn** (*laminae* 1-2): it contains the Marginal *nucleus* and the *substantia gelatinosa.*
- **Intermediate dorsal horn** (*lamina* 3)
- **Deep dorsal horn** (*laminae* 4-6): it includes the *Proprius* and *Reticular nuclei.*

Lateral horn (lamina 7)

The lateral horn acts as a central hub in which visceral, proprioceptive and descending supraspinal signals converge. It contains preganglionic sympathetic neurons within the intermediolateral and the intermediomedial column (C8-L2), as well as the parasympathetic preganglionic neurons within sacral parasympathetic nuclei (S2-S4). Furthermore, in this region there is the Clarke's column, origin of the dorsal spinocerebellar tract, which plays a crucial role in transmitting proprioceptive information required for cerebellar coordination. More ventrally, the spinal gray matter also houses Renshaw cells, a specialized population of inhibitory interneurons involved in the modulation of motor neuron activity and the regulation of spinal motor output (5).

Ventral horn (laminae 8 and 9)

The ventral horn is composed by *laminae* 8 and 9, which play a key role in motor control. The first one contains interneurons involved in contributing posture and locomotion, while the last hold α- and γ-motoneurons whose axons innervate skeletal muscle fibers and muscle spindles.

Central gray matter (lamina 10)

It corresponds to the *lamina* 10 and it is made up of interneuron participating in visceral afferences, neurons involved in autonomic integration and fibres decussating in order to synchronize the bilateral spinal networks.

1.1.3 Spinal white matter organization

Surrounding the spinal gray matter is the white matter, a region composed of myelinated and unmyelinated nerve fibers organized into ascending and descending tracts responsible for transmitting sensory and motor information between the SC and the brain. The white matter can be anatomically subdivided into anterior, posterior and lateral columns. Instead, functionally it can be divided into ascending, descending and propriospinal pathways. From a clinical point of view, it is useful to focus on the first two pathways (2).

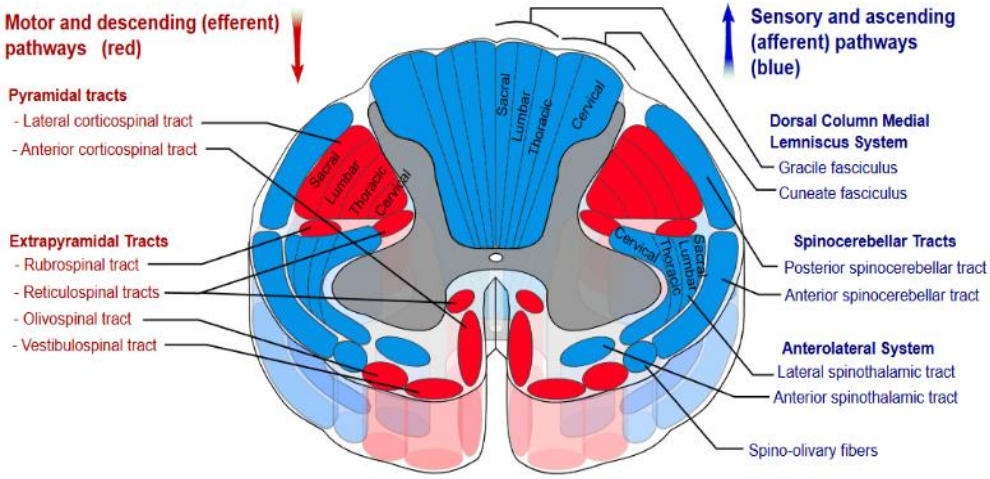


Figure 5: pathways of SC.
Source: https://en.wikipedia.org/

Ascending tracts

They include the dorsal column-medial lemniscus pathways (DCML), the anterolateral system (ALS) and the spinocerebellar tracts.

In the DCML, the primary neuron axons enter the SC and ascend in the dorsal columns. Fibers from below T6 travel medially in the *gracile fasciculus*, while fibers from above T6 ascend laterally in the *cuneate fasciculus*. These first-order neurons continue up to the medulla, where they synapse in the *nucleus gracilis* or *nucleus cuneatus*. The second-order neurons then cross the midline as internal arcuate fibers and ascend on the opposite side as the medial lemniscus. Lastly, they reach the ventral posterolateral (VPL) nucleus of the thalamus, where they synapse with third-order neurons. These final neurons project through the posterior limb of the internal capsule to the primary somatosensory cortex.

The ALS is characterised by the primary neuron axons entering the SC and ascending to 1 or 2 levels (Lissauer's tract), where they synapse with the secondary neurons in the *substantia gelatinosa*. The second order neurons decussate and climb up laterally in the spinothalamic tract. Eventually, they synapse at the ventral posterolateral (VPL) nucleus of the thalamus. The axons of the tertiary neurons travel to the primary sensory cortex via the posterior limb of internal capsule.

Eventually, the spinocerebellar tracts carry proprioceptive information, and they are composed by three main portions: ventral spinocerebellar (below L2), dorsal spinocerebellar (from L2 to T1) and cuneo-cerebellar (above T1) tracts.

Descending tracts

Descending tracts carry motor signals from the brain to the muscles and involve two neurons: an upper motor neuron (UMN) and a lower motor neuron (LMN). The UMN originates in the brain and descends to the SC, where it synapses with an LMN in the ventral horn. The LMN, then, sends fibers out through the spinal roots to reach skeletal muscles. They are represented by corticospinal, rubrospinal, vestibulospinal, reticulospinal and tectospinal tracts.

In the corticospinal tract the UMN arise from motor and sensory cortical areas (Brodmann areas 1, 2, 3, 4, and 6). Their axons pass through the internal capsule, cerebral peduncles, pons, and medullary pyramids. About 90% of fibers cross at the pyramidal decussation and descend as the lateral corticospinal tract, while the remaining continue ipsilaterally as the anterior corticospinal tract. The lateral corticospinal tract controls fine voluntary movements of distal limbs, whereas the anterior corticospinal tract control axial and proximal muscles.

The rubrospinal tract descends alongside the lateral corticospinal tract and it controls the flexor muscles facilitating the flexion and simultaneously inhibiting the extensor muscles.

The vestibulospinal tract is crucial for balance, antigravity posture and head-eye coordination. Its fibers originate from the vestibula nuclei in the brainstem.

The reticulospinal tract comes from the pontine medullary reticular formation and it regulates posture, locomotor patterns and muscular tone.

The tectospinal tract departs from the superior colliculi and it is responsible for the reflexive orientation of the head and neck to visual or auditory stimuli.

1.2 Nerves fibers

Sensory information deriving from the skin, skeletal muscles and joints is conveyed to the SC by primary sensory neurons whose cell bodies reside in the dorsal root ganglia. Before penetrating the SC, each dorsal root axon bifurcates into ascending and descending branches, influencing multiple spinal segments above and below its level of entry. Then, motor and visceral efferent fibers leave the SC via the ventral roots. These fibers arise from somatic motoneurons located in the ventral horn and from preganglionic autonomic neurons within the intermediolateral cell column. The α-motoneurons innervate extrafusal skeletal muscle fibers and are responsible for force generation, whereas γ-motoneurons supply intrafusal muscle spindle fibers, thereby modulating muscle tone and proprioceptive feedback. Visceral motoneurons transmit preganglionic fibers to autonomic ganglia, thereby influencing internal organ function. Dorsal and ventral roots join together into the intervertebral foramen to form a mixed spinal nerve containing both sensory and motor components. Each spinal nerve subsequently divides into

dorsal and ventral primary *rami*. The dorsal *ramus* supplies the skin and intrinsic muscles of the back; instead, the ventral *ramus* innervates the anterolateral trunk, the limbs, and contributes to autonomic distribution to visceral structures (2).

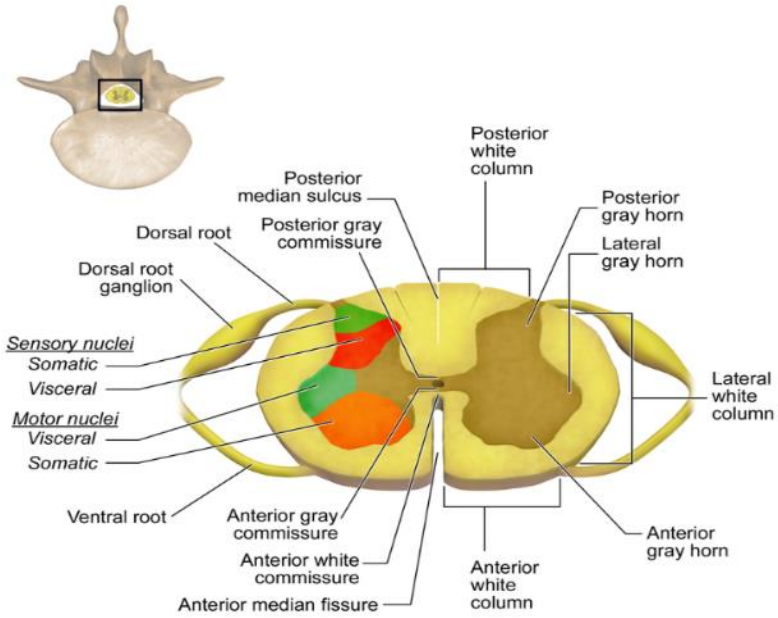


Figure 6: Organization of grey and white matter of SC with the sensory, the motor and the autonomic pathways (cross-section).
Source: https://courses.lumenlearning.com/

1.2.1 Nerve fibers classifications

The nerve fibers are categorized according to different criteria:

1) Erlanger-Gasser classification

It is based on electrophysiological characteristics of nerve fibers (diameter, conduction velocity and grade of myelination).

Table 1: Erlanger-Gasser classification

Fiber Type	Myelination	Diameter (µm)	Conduction velocity (m/s)	Main function
Aα	Heavily myelinated	13-20	80-120	Skeletal muscle motricity, proprioception
Aβ	Myelinated	6-12	35-75	Touch, pressure, vibration
Aγ	Myelinated	3-6	15-35	Muscle spindles regulation
Aδ	Thinly myelinated	1-5	5-30	Fast pain, temperature (cold), crude touch

B	Lightly myelinated	<3	3-15	Preganglionic autonomic fibers
C	Unmyelinated	0.2-1.5	0.5-2	Slow pain, temperature (warmth), itch; postganglionic autonomic fibers

2) Lloyd-Hunt classification

It's a functional classification which divide the fibers according to the information that they carry (motor, sensitive, autonomic). This labelling is related to that of Erlanger-Gasser previously discussed.

Table 2: Lloyd-Hunt classification

Fiber Type	Corresponds to Erlanger-Gasser	Diameter (µm)	Conduction velocity (m/s)	Origin/function
Group Ia	Aα	13-20	80-120	Primary muscle spindle afferents (dynamic stretch)
Group Ib	Aα	13-20	80-120	Golgi tendon organ afferents (tension)
Group II	Aβ	6-12	35-75	Secondary muscle spindle afferents (static stretch)
Group III	Aδ	1-5	5-30	Fast pain, temperature
Group IV	C	0.2-1,5	0.5-2	Slow pain, metabolic/muscle nociception

1.3 Spinal cord reflexes: organization and role in motor control

1.3.1 Anatomical basis of proprioceptive reflexes

Within muscles there are several types of sensory receptors that inform the CNS about the functional state of the muscle: these are the neuromuscular spindles and Golgi tendon organs (2).

The neuromuscular spindles

Muscle spindles are encapsulated proprioceptive receptors composed of specialized intrafusal fibers, including nuclear bag (dynamic and static) and nuclear chain fibers. They receive both sensory and motor innervation: group Ia afferents form primary endings and encode muscle length and stretch velocity, whereas group II afferents form secondary endings and primarily signal sustained muscle length. Their sensitivity is regulated by dynamic and static γ-motoneurons, which innervate specific intrafusal fiber types and adjust spindle responsiveness to stretch. By detecting both active and passive muscle elongation, muscle spindles provide essential proprioceptive feedback and mediate the stretch reflex, facilitating activation of agonist muscles while inhibiting antagonists (6).

The Golgi tendon organs

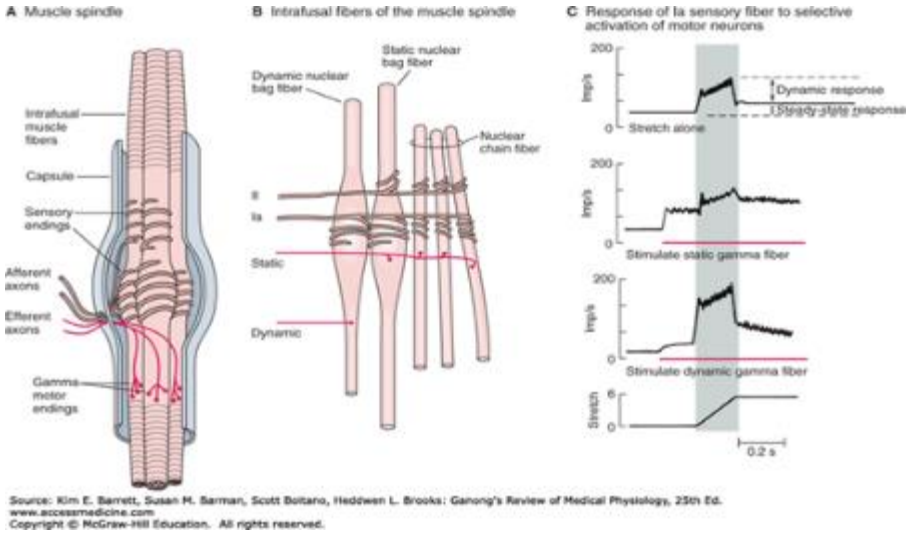


Figure 7: ***(A)*** *The muscle spindle structure and organization.* ***(B)*** *The three distinct types of intrafusal fibers that are present in the spindle: dynamic nuclear bag fibers, static nuclear bag fibers, and nuclear chain fibers.* ***(C)*** *The response pattern of Ia sensory fibers.*
Source: Barrett, K. E., Barman, S. M., Boitano, S., & Brooks, H. L. Ganong's Review of Medical Physiology, 25th Edition.

The Golgi tendon organs consist of group Ib afferent (Aα) fibers that branch extensively within a connective tissue capsule and are located at the musculotendinous junction. Their activation is determined by an increase in tendon tension, and this determines an inhibition of the agonist muscles and an activation of the antagonists in order to prevent excessive muscle tension that could cause a tear of the muscle itself. The discharge pattern of Ia afferent fibers varies depending on γ-motor neuron activity. During passive muscle stretch without γ-activation, Ia fibers exhibit a modest dynamic response at the onset of stretch followed by a moderate increase in steady-state firing proportional to muscle length. Activation of static γ-motor neurons enhances the steady-

state discharge while attenuating the dynamic component, increasing sensitivity to maintained muscle length. Conversely, stimulation of dynamic γ-motor neurons markedly amplifies the dynamic response at the onset of stretch, while the steady-state firing gradually returns toward baseline levels. This functional differentiation allows differentiation allows the CNS to selectively adjust spindle sensitivity to either the velocity or the magnitude of muscle stretch (7).

1.3.2 Reflex circuits

The SC is organized into complex and precisely structured reflex networks that form the basic framework for sensorimotor integration. Foundational studies conducted by Sherrington, Eccles, and subsequently Lundberg, in which they used intracellular recordings to discover the organization of neuronal networks in the cat SC, demonstrated that spinal reflexes should not be viewed as simple, independent responses (8). Rather, they represent essential elements of motor control, continuously shaped and adjusted according to behavioural goals, task requirements, and the dynamic functional state of spinal circuitry. Five different types of pathways were described (9).

Recurrent inhibition

Recurrent inhibition has always been related to the scientist Renshaw since it involves Renshaw neurons (inhibitory interneurons). Then, Eccles' studies, based on electrophysiological and pharmacological analysis of recurrent inhibition, allowed to demonstrate that it was a disynaptic circuit relied on a cholinergic synapse formed by collaterals of motor axons Renshaw cells. These interneurons, in turn, applied an inhibitory effect on motoneurons, mediated by glycine, and producing a postsynaptic hyperpolarization. The strength of recurrent inhibition was found to vary according to functional relationships between motor pools. It was particularly pronounced among motoneurons supplying muscles that act synergistically, especially within the homonymous motor nucleus. Conversely, inhibitory interactions between motor nuclei controlling antagonistic muscles were largely absent. Furthermore, motoneurons exhibiting longer after hyperpolarization durations, typically those associated with slow-twitch motor units, received more substantial recurrent inhibitory input than those innervating fast-twitch muscle fibers. With weak contractions, recurrent inhibition was stronger, but with increasingly strength of contractions the recurrent inhibition did not improve in parallel. This led to the conclusion that recurrent inhibition is not static, and it varies, highlighting its role in fine-tuning the motor output depending on the contraction intensity and on the task demands. (10,11)

Stretch reflex

The stretch reflex is a monosynaptic reflex which consists of an automatic contraction of the muscle when it is stretched, and it is mediated by the Ia muscle spindles fibers. This reflex is responsible of the activation of homonymous motoneurons. This pathway relies on a mechanism of reciprocal inhibition in which stimulation of the agonist motor neuron is associated with inhibition of the antagonist muscle motor neuron. Application of this paradigm revealed that transmission within the disynaptic reciprocal inhibitory circuit to antagonist motoneurons is enhanced during voluntary contraction of the agonist muscle suggesting the existence of an important central facilitatory effect in such a way as to allow a fluid and finely regulated movement during voluntary activity and locomotion. Several studies have reported a decrease in the activity of this inhibitory pathway in patients with spasticity due to different aetiologies, particularly in the case of SCI (9).

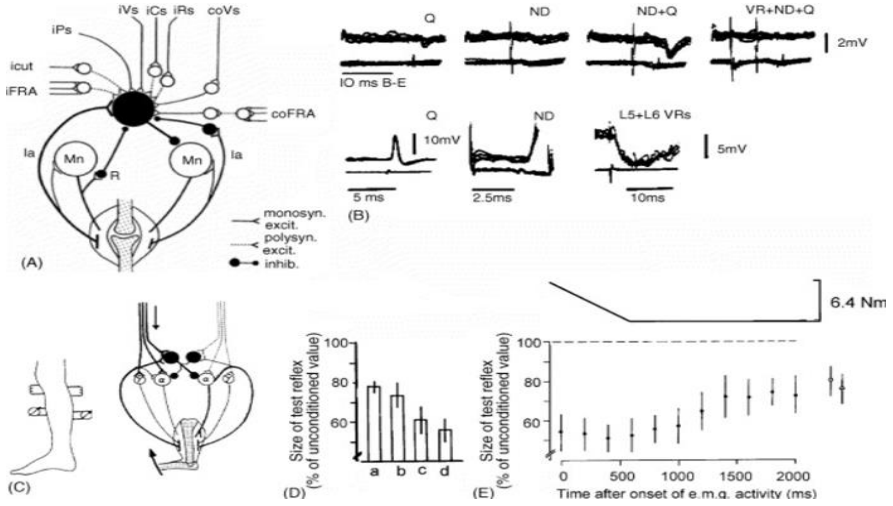


Figure 8: Reciprocal Ia inhibition, spinal circuitry and task-dependent modulation during voluntary movement.
***(A)** Schematic representation of the spinal circuitry underlying reciprocal Ia inhibition.*
***(B)** Experimental recordings in the cat demonstrate convergent excitation and recurrent inhibition of Ia inhibitory interneurons. Intracellular recordings from a knee flexor motoneuron show IPSPs triggered by stimulation of quadriceps Ia afferents (Q) and Deiters' nucleus (ND), with enhanced inhibition when both inputs are combined (spatial facilitation). Conditioning stimulation of the L5–L6 ventral roots reduces the IPSP amplitude, indicating recurrent inhibition mediated by Renshaw cells. Direct recordings from Ia inhibitory interneurons confirm monosynaptic excitation from Q and ND and a delayed disynaptic IPSP following ventral root stimulation.*
***(C)** During voluntary dorsiflexion descending motor commands activate α- and γ-motoneurons of the agonist muscle, while simultaneously exciting Ia inhibitory interneurons suppress antagonist motoneurons ensuring coordinated movement.*
***(D-E)** In humans, reciprocal inhibition is modulated in a task- and time-dependent manner. The conditioned soleus H-reflex progressively decreases before and at the onset of tibialis anterior EMG activity, demonstrating anticipatory, centrally driven enhancement of antagonist inhibition during voluntary dorsiflexion.*
Source: Hultborn H. (2006). Spinal reflexes, mechanisms and concepts: from Eccles to Lundberg and beyond. Progress in neurobiology, 78(3-5), 215–232.

Reflex pathways from Golgi tendon organs

The Golgi tendon organ is described as mediating the inhibitory autogenic reflex, via the afferent fibers of group Ib, with the aim of to protect the muscle from excessive tension. However, later, Hongo and Lundberg showed that interneurons Ib are not only responsible for the inhibitory autogenic reflex, but are part of a more complex integrative circuit (group I non-reciprocal inhibition) characterized by the convergence of fibers Ia, rubrospinal pathways, skin afferences, etc. When the locomotor networks are active, Ib afferent input no longer primarily exerts inhibition on motoneurons; instead, it produces a functional excitatory drive contributing to load-dependent control of stance known as the reflex reversal. This phenomenon proves the flexible and state-depending nature of the SC network (7,12,13)

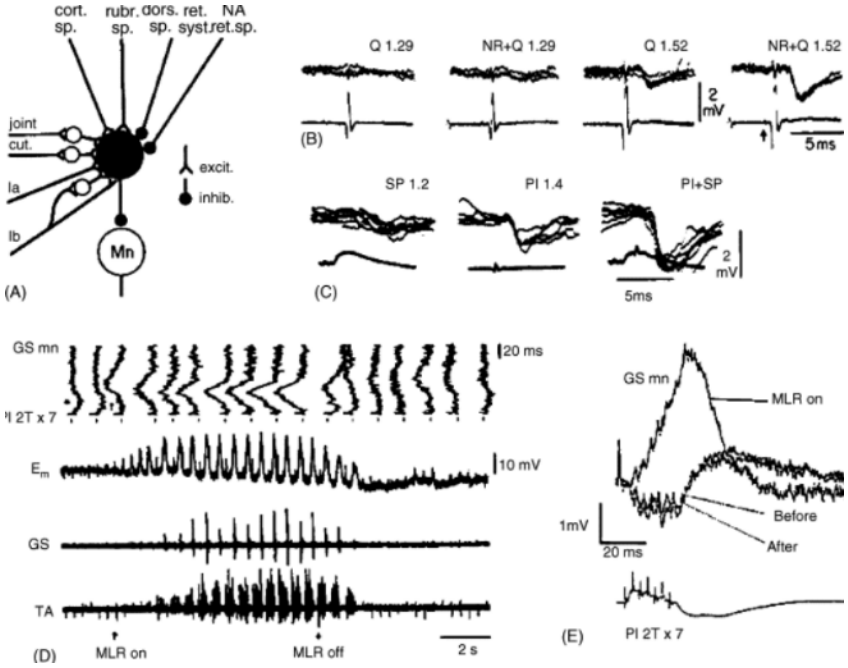


Figure 9: Convergence onto Ib inhibitory interneurons and state-dependent modulation of group I input during fictive locomotion.
(A) Simplified diagram illustrating the main synaptic inputs to Ib inhibitory interneurons.
(B) Intracellular recordings show facilitation between rubrospinal input and quadriceps group I afferents; this interaction appears only when stimulation intensity is sufficient to recruit Ib fibers.
(C) Similar facilitatory effects are observed between cutaneous afferents (superficial peroneal nerve) and group I input from the plantaris nerve, indicating multisource convergence onto the Ib pathway.
(D–E) Recordings from a gastrocnemius–soleus motoneuron demonstrate that group I stimulation produces classical inhibitory responses before locomotion, but evokes excitatory postsynaptic potentials during MLR-induced fictive locomotion. Averaged traces confirm this state-dependent shift, highlighting the functional reorganization of group I input during locomotor activity.
Source: Hultborn H. (2006). Spinal reflexes, mechanisms and concepts: from Eccles to Lundberg and beyond. Progress in neurobiology, 78(3-5), 215–232.

Flexor withdraw reflex

The flexor reflex afferents (FRA) set up spinal network of interneurons that integrates group II and III muscle afferents, joint afferents, and cutaneous afferents eliciting polysynaptic responses conforming to the classical flexion and crossed-extension pattern. Despite their heterogeneous receptor origin and broad receptive fields, these afferents exert a common functional effect, most likely through convergence onto shared populations of spinal interneurons. Experimental evidence further demonstrated that transmission within FRA pathways is strongly state-dependent: in decerebrate preparations, reflex transmission may be tonically suppressed or even reversed, whereas spinal transection restores the excitatory flexor pattern, indicating powerful supraspinal modulation of these circuits. These findings led Lundberg to propose that the extensive multisensory convergence onto FRA-related interneurons provides access to alternative reflex pathways whose selection depends on descending motor commands. In this framework, diffuse sensory inflow can be selectively channelled to reinforce the spinal circuitry engaged by ongoing voluntary activity. Notably, FRA cannot be equated with nociceptors, as their capacity to evoke flexor reflex activity is not restricted to noxious stimulation. This organizational principle stands in contrast to the classical nociceptive flexor withdrawal reflex described by Charles Scott Sherrington, which is characterized by modality-specific cutaneous input, somatotopic representation in the dorsal horn, and a well-defined withdrawal response. It consists of the activation of ipsilateral flexor muscles and inhibition of the extensors to rapidly withdraw a potentially harmful stimulus. Whereas the latter reflects a highly structured and stimulus-bound protective reflex, FRA pathways exemplify a context-dependent, dynamically regulated spinal feedback system integrated with supraspinal motor control (14).

Presynaptic inhibition

Presynaptic inhibition represents a key modulatory mechanism within spinal sensorimotor networks, regulating the impact of primary afferent input before it influences postsynaptic neurons. In contrast to postsynaptic inhibition, which alters the membrane potential of motoneurons or interneurons directly, presynaptic inhibition operates at the central terminals of primary afferent fibers (primarily group Ia muscle spindle afferents) thereby adjusting neurotransmitter release at the synaptic level. This process is mediated by specialized axo-axonic GABAergic interneurons whose activation produces primary afferent depolarization (PAD). Functionally, this mechanism acts as a dynamic gain control system, shaping reflex amplitude, preventing excessive excitation, and enabling context-dependent filtering of sensory feedback. Importantly, presynaptic inhibition is strongly regulated by descending supraspinal pathways, which can either enhance or suppress transmission in specific afferent populations. During

voluntary movement, this descending control makes presynaptic inhibition highly selective: Ia input to motoneurons participating in the voluntary motor task is relatively disinhibited, whereas afferent feedback to non-engaged muscles is suppressed. Thus, a mechanism that appears anatomically widespread becomes functionally focused, ensuring that proprioceptive feedback reinforces the appropriate motor output (14).

These findings underscore that the SC operates as an adaptive sensorimotor integrator rather than a passive relay. Reflex transmission is continuously shaped by descending commands, behavioural context, and intrinsic network state. Following SCI, the interruption of supraspinal modulation profoundly alters this balance. The reduction of descending control diminishes presynaptic inhibition and unmasks intrinsic spinal excitability, resulting in enhanced afferent transmission and exaggerated reflex gain. Under these conditions, normally adaptive networks, such as the flexor reflex afferent (FRA) system, may become disinhibited and hyperresponsive, allowing otherwise innocuous sensory inputs to trigger widespread, multi-segmental motor activity. Clinically, this maladaptive reorganization contributes to hyperreflexia, poorly coordinated flexor spasms, and the development of spasticity.

1.4 Spinal Cord Injury (SCI)

1.4.1 Epidemiology

Spinal cord injury (SCI) is a life-altering, shattering condition that causes major motor, sensory and autonomic dysfunctions related with permanent disability, dependency, and psychological stress. The global rate of SCI stands around at 250 000-500 000 individuals every year. A major impact is represented by traumatic SCI. The most frequent causes include motor vehicle accidents (36–48%), acts of violence (5–29%), falls (17–21%), and sports or recreational activities (7–16%). The mean age at the time of injury is approximately 31.7 years, with the highest incidence observed among individuals aged 15–25 years. Males are disproportionately affected, with a male-to-female ratio of roughly 4:1. The economic burden of traumatic SCIs is considerable, with direct annual healthcare costs in the USA exceeding $7 billion. In contrast, the true prevalence of non-traumatic SCIs remains uncertain due to their heterogeneous aetiologies (ischaemic, degenerative, tumours, congenital and developmental, etc) and the lack of comprehensive national registries (15).

1.4.2 Pathophysiology of SCI

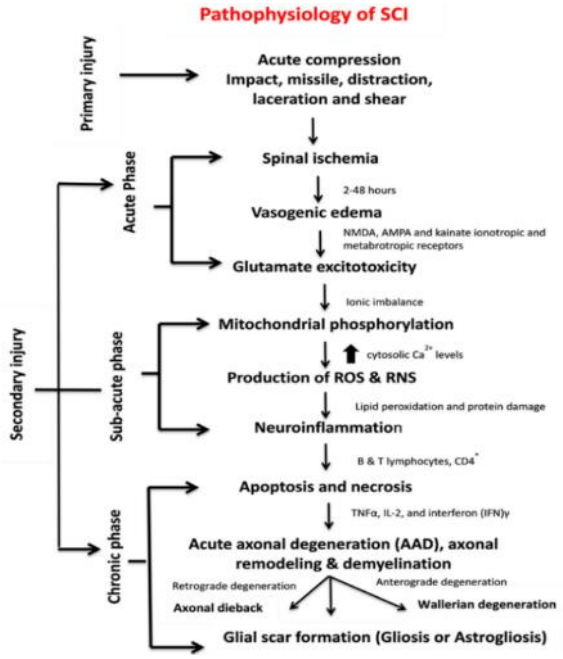


Figure 10: Pathophysiology of SCI.
Source: Anjum, A., Yazid, M. D., Fauzi Daud, M., Idris, J., Ng, A. M. H., Selvi Naicker, A., Ismail, O. H. R., Athi Kumar, R. K., & Lokanathan, Y. (2020). Spinal Cord Injury: Pathophysiology, Multimolecular Interactions, and Underlying Recovery Mechanisms. International Journal of Molecular Sciences, 21(20), 7533.

Normal function in SC is characterised by the interaction of different cell types, such as neurons, neuroglia, and non-neural cells. After SCI, these multicellular interactions are interrupted and disorganized, leading to an impaired spinal recovery (16–18).

Primary injury

The initial stage immediately after the injury is defined as primary injury and it results from fractures, bone dislocation and spinal ligament tearing. This phase involves disruption of neural parenchyma and axonal networks, blood vessels damage, micro-haemorrhages in the central gray matter and secondary ischaemia deriving from the SC exceeding venous blood pressure. The main determinants for SC severity are the extension of initial destruction and the duration of SC compression (15).

Secondary injury

The initial mechanical insult triggers a complex cascade of secondary injury mechanisms that begin within minutes after trauma and may evolve over days to weeks. Cellular and vascular disruption at the lesion site lead to the release of neurotoxic mediators, as for instance the excessive extracellular glutamate, inducing a massive influx of calcium ions. Consequently, intracellular calcium overload activates deleterious pathways which amplify cellular damage, including mitochondrial dysfunction, protease and phospholipase activation, and the generation of ROS. In addition, a robust inflammatory response occurs exacerbating the tissue injury through the release of cytokines, chemokines, and proteolytic enzymes. Concurrently, vascular dysregulation, including vasospasm and microthrombus formation, impairs SC perfusion and perpetuates ischaemia. Based on their temporal evolution, secondary injury mechanisms are typically classified into three phases:

- **Acute phase:** characterized by vascular disruption, ionic imbalance, excitotoxicity, calcium overload, free radical generation, lipid peroxidation, inflammation, edema, and tissue necrosis.
- **Subacute phase:** marked by neuronal apoptosis, axonal demyelination, Wallerian degeneration, axonal remodelling, and the progressive development of the glial scar.
- **Chronic phase:** characterized by cystic cavity formation, axonal dieback, and maturation of the glial scar.

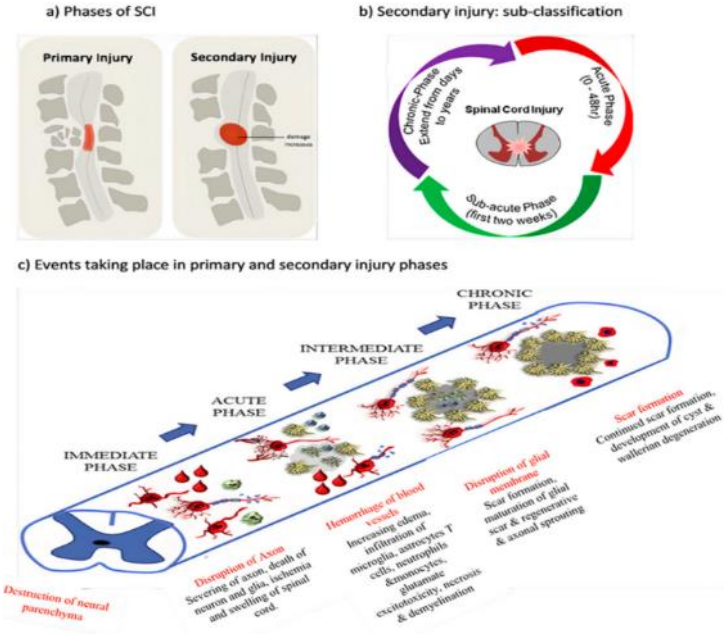


Figure 11: Spinal cord injury (SCI). ***(A)*** *phases of SCI.* ***(B)*** *Sub-classification of secondary injury depending on duration of injury.* ***C)*** *The pathophysiological events in relation to SCI phases. Source: Anjum, A., Yazid, M. D., Fauzi Daud, M., Idris, J., Ng, A. M. H., Selvi Naicker, A., Ismail, O. H. R., Athi Kumar, R. K., & Lokanathan, Y. (2020). Spinal Cord Injury: Pathophysiology, Multimolecular Interactions, and Underlying Recovery Mechanisms. International journal of molecular sciences, 21(20), 7533.*

These changes generate a microenvironment that is highly unfavourable to axonal regrowth, thereby markedly restricting endogenous repair and spontaneous functional improvement. Unlike the primary mechanical insult, the secondary injury phase provides the principal therapeutic window for neuroprotective interventions aimed at limiting tissue damage and improving neurological outcomes. Prompt regulation of the underlying molecular and cellular cascades may limit secondary tissue damage, reduce lesion spread, and safeguard surviving neural structures, thereby enhancing the prospects for functional recovery (17–20).

1.4.2.1 Compartmental organization of SCI lesions

The SCI lesions are made up by three different tissue compartments (respectively the non-neuronal lesion core, the astrocyte scar border and the spared reactive neural tissue) which exhibit different cellular composition and network (17,19,20).

Non-neuronal lesion core

Subsequently to cellular damage resulting from SCI, within the non-neuronal lesion core there is a robust proliferation of perivascular fibroblast-derived stromal cells, meningeal fibroblasts, and pericytes. As debris is progressively removed and the lesion stabilizes, the core becomes predominantly populated by these non-neural stromal elements, together with endothelial

progenitor cells and newly formed vasculature and infiltrating blood-derived cells. Although inflammatory infiltrates typically decline during later stages, their sustained presence may continue to promote secondary tissue damage.

Astrocyte scar border

The formation of the astrocyte scar border begins within 1-2 days after the SCI, and it continues for 7-10 days. This compartment is composed almost entirely by newly proliferated astrocytes and functionally and structurally it is similar to glia limitans. The aim of the astrocyte scar border is to isolate the damaged tissue and preserve the adjacent viable neural tissue preventing the extension of the pathological process.

Spared reactive neural tissue

The spared reactive neural tissue contains normally functional neural tissue with the difference that it has hypertrophic astrocytes. The structurally preserved yet biologically reactive tissue exhibits marked synaptic remodelling, with active synapse elimination and formation accompanied by significant reorganization of local and distributed neural circuitry.

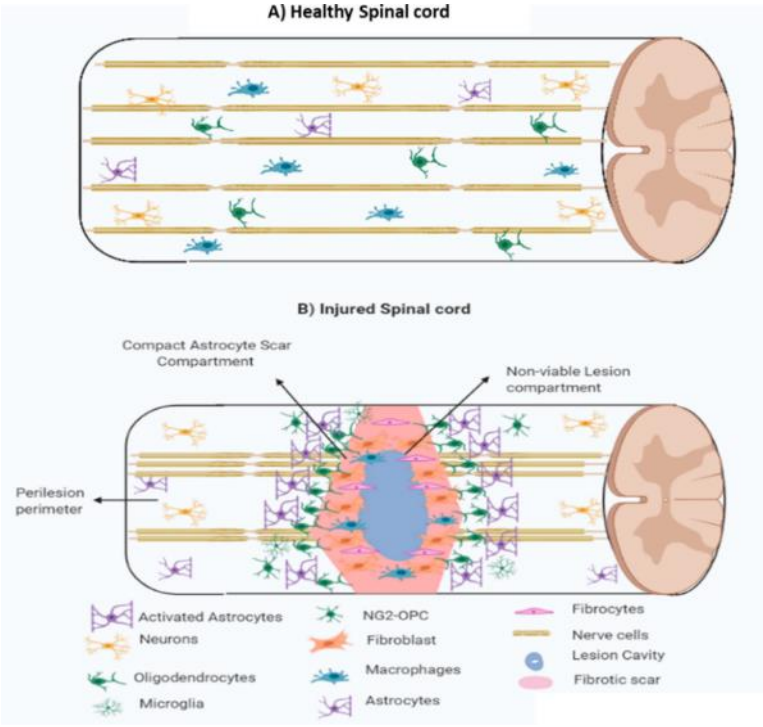


Figure 12: Comparison between healthy SC and injured SC. ***(A)*** *Healthy spinal cord.* ***B)*** *Injured spinal cord with three lesion compartments (inner non-viable small lesion compartment, compact astrocyte core, and peri-lesion perimeters with multicellular and multi-molecular components).*
Source: Anjum, A., Yazid, M. D., Fauzi Daud, M., Idris, J., Ng, A. M. H., Selvi Naicker, A., Ismail, O. H. R., Athi Kumar, R. K., & Lokanathan, Y. (2020). Spinal Cord Injury: Pathophysiology, Multimolecular Interactions, and Underlying Recovery Mechanisms. International journal of molecular sciences, 21(20), 7533.

Anatomically complete SCI results from either a single extensive lesion or multiple smaller lesions that collectively transect the full cross-sectional area of the SC, thereby abolishing neural continuity across the lesion site. In such cases, the injury is also functionally complete, with total loss of voluntary motor output and sensory transmission below the lesion. In contrast, anatomically incomplete SCI involves partial preservation of spinal tissue, maintaining residual axonal pathways across the lesion. This spared substrate may sustain the spontaneous reformation of supraspinal or propriospinal connectivity. Consequently, incomplete injuries are associated with variable degrees of retained or recovered function, although in some cases the remaining connections are insufficient to support meaningful motor or sensory activity, resulting in a functionally complete presentation despite anatomical sparing.

1.4.2.2 Spontaneous circuit reorganization

Raisman was the first to demonstrate that after injury-induced loss of synapses in the forebrain there were the production of new synapses formed by survival local terminals. This process of circuit reorganization occurs all forms of CNS injuries and could lead to adaptive or maladaptive changes. After a SCI, in some cases the circuit reorganization can induce a maladaptive cascade leading to muscle spasticity, neuropathic pain (NP) and autonomic disorders. In other cases, conversely, this circuit rearrangements can be adaptive and determines the functional recovery, such as in unilateral SC hemi-section or in Brown-Séquard syndrome. Elucidating the cellular and molecular processes that drive post-injury plasticity and identifying strategies to selectively enhance adaptive while limiting maladaptive circuit reorganization, represent critical objectives in SCI research. Several mechanisms are involved in spontaneous circuit reorganization as discussed below (21).

CNS neurons lose their intrinsic capacity to grow axons as they mature and exhibit poor reactivation of intrinsic programs for axon growth. However, some studies showed that after SCI the signalling through PTEN, mTOR, STAT3, and SOCS3 pathways could intrinsically regulates the axon-regenerative capacity of retinal and corticospinal neurons (22–25).

After SCI, axon regrowth is regulated by the interaction of multiple cell types located in different lesion compartments. Reactive astrocytes within the glial scar and spared tissue can either restrict or, under appropriate growth conditions, support axonal regeneration through extracellular matrix molecules such as laminin (26). NG2-expressing oligodendrocyte progenitor cells are also present at scar borders, although their role remains controversial, with evidence supporting both inhibitory and permissive effects on axonal growth (27,28). In the lesion core, pericytes and fibroblast-lineage cells produce extracellular matrix components, including collagens and chondroitin sulphate proteoglycans, which generally inhibit axonal extension (29). Finally, immune cells exert context-dependent effects, as activated macrophages may promote axonal

dieback, whereas neutrophils located near neuronal soma may enhance regenerative responses. The axonal regrowth is further governed by a tightly regulated balance of environmental molecular cues. Pro-regenerative signals include diffusible chemoattractants such as neurotrophic factors (e.g., BDNF, NT-3, and GDNF), which are markedly reduced after injury and thereby limit spontaneous regeneration, as well as contact-mediated attraction driven by extracellular matrix (ECM) components such as laminins and heparan sulphate proteoglycans (30,31). In parallel, axonal growth is constrained by both diffusible chemorepulsive cues, including Wnt proteins, semaphorins, and netrins combined with contact-mediated inhibitory factors, such as myelin-associated proteins and chondroitin sulphate proteoglycans, which together hinder long-distance regeneration while promoting local circuit remodelling (32–35).

Within this same post-injury milieu, synaptic organization is also profoundly reshaped through coordinated multicellular mechanisms. Microglia actively participate in synaptic pruning via complement-dependent pathways, removing damaged or unnecessary synapses, whereas astrocytes modulate synaptic formation and network organization through the release of synaptogenic factors (thrombospondins, glypicans, hevin), axon guidance cues (semaphorin-3A), and extracellular matrix components involved in perineuronal net formation. These perineuronal nets, rich in chondroitin sulphate proteoglycans, act as structural barrier on synaptic reorganization, although their inhibition or targeting of associated pathways (NOGO signalling) can enhance plasticity in spared spinal circuits (36,37).

Thereby, functional improvements observed after incomplete SCI are increasingly thought to arise primarily from the reorganization of existing neural circuits rather than from long-distance axonal regeneration across the lesion site.

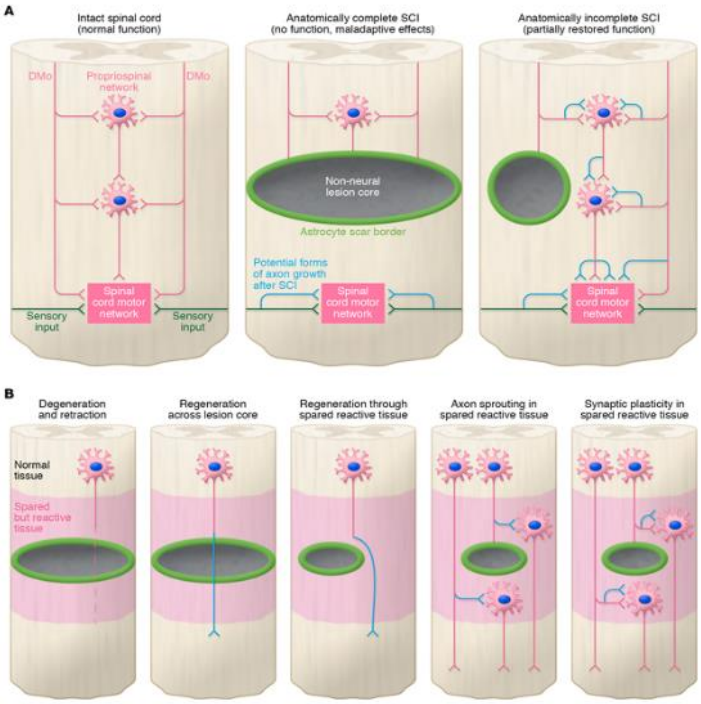


Figure 13: Circuit reorganization after SCI.
***A)** Different types of circuit reorganization after different types of SCI (complete vs incomplete). In incomplete SCIs, residual descending pathways and propriospinal networks provide a structural basis for adaptive plasticity, enabling sensory input to be harnessed toward functional motor recovery. By contrast, complete lesions lead to functional isolation of spinal circuits below the injury. In the absence of supraspinal modulation, subsequent reorganization tends to be maladaptive, promoting neuronal hyperexcitability and the emergence of spasticity rather than coordinated motor output.*
***B)** Different potential growth responses of axons and synapses after SCI.*
Source: O'Shea, T. M., Burda, J. E., & Sofroniew, M. V. (2017). Cell biology of spinal cord injury and repair. The Journal of clinical investigation, 127(9), 3259–3270.

1.4.3 Clinical presentations

The clinical presentation of SCI varies according to the anatomical level of the lesion, the nature of the traumatic event, and the extent of neural tissue damage. Typically, SCI is characterized by a constellation of motor, sensory, and autonomic impairments affecting body regions located below the site of injury frequently associated with complex respiratory and cardiovascular disturbances that may pose an immediate threat to life. These alterations require prompt medical management in order to prevent further neurological deterioration and to reduce the risk of serious complications and overall morbidity (38,39).

Acute complications

1. Neurogenic and hypovolemic shock

In the early phase following SCI, disruption of autonomic regulation can lead to neurogenic shock, a condition characterized by depressed reflex activity and a marked imbalance between sympathetic and parasympathetic control when the lesion occurs above the T6 level. This predominance of parasympathetic system causes several systemic manifestations, including bradycardia, neurogenic orthostatic hypotension (OH), bronchial constriction, increased airway secretions, and priapism, in addition to the motor and sensory deficits caused by the injury itself. At the same time, traumatic SCI is frequently associated with hypovolemic shock due to haemorrhage from concomitant injuries. Although, blood loss would normally trigger a compensatory increase in heart rate (HR), but in these patients this response may be blunted by the impaired sympathetic activity. In case of cervical or high thoracic lesions, pronounced bradycardia can significantly compromise cardiac output (40,41).

2. Spinal shock

Spinal shock refers to a temporary physiological suppression of SC function that occurs immediately after the injury to any level of the SC. This condition may persist for several days or weeks following trauma. Clinically, it is commonly associated with areflexia, including absence of the bulbocavernosus reflex, as well as flaccid paralysis, urinary retention and bladder distension. Although the exact timeline of reflex recovery remains debated, the reappearance of spinal reflexes generally indicates the resolution of the shock phase. It must be differentiated from the neurogenic shock which is substantially a distributive shock due to the loss of sympathetic activity (40,41).

3. Cardiovascular dysfunction

High cervical and upper thoracic SCI significantly disrupt autonomic cardiovascular regulation due to impaired sympathetic outflow as discussed above. Unopposed vagal activity at the sinoatrial and atrioventricular nodes commonly leads to neurogenic bradycardia and may increase the risk of atrioventricular conduction disturbances. Even during physical exertion, the absence of adequate sympathetic stimulation limits the ability to increase HR, with peak values rarely exceeding 120 beats per minute. In addition, reduced sympathetic vasomotor control causes widespread vasodilation, as activation of vascular α1-adrenergic receptors is diminished. This impairment compromises the capacity to maintain vascular tone and blood pressure, frequently resulting in neurogenic OH. The loss of sympathetic regulation also reduces venous tone, promoting venous pooling in the lower extremities, particularly in the presence of paralysis and

the absence of normal muscle pump activity. Consequently, venous return and left ventricular end-diastolic volume are reduced, leading to decreased preload and diminished myocardial contractility through the Frank–Starling mechanism. These hemodynamic alterations may can predispose individuals with SCI to dizziness or syncope, especially during upper limb exertion (40–42).

4. Respiratory dysfunction

The high SCI significantly impair respiratory function through disruption of sympathetic control and paralysis of key respiratory muscles which manifest themselves respectively with bronchoconstriction, airway hyperreactivity, increased mucus secretion, a neurogenic restrictive ventilatory pattern and a marked weakening of the cough reflex, impairing the ability to clear airway secretions. Consequently, these patients are particularly susceptible to pulmonary complications such as atelectasis, pneumonia, and mucus plugging. Respiratory failure may also arise from direct injury to structures involved in ventilation, including the cervical SC segments responsible for diaphragmatic innervation (C3–C5) and the thoracic roots supplying accessory respiratory muscles (T1–T11). Complete lesions above C3 typically result in immediate ventilatory failure, whereas subjects with partial high-cervical injuries (C3–C5) may initially maintain ventilation through accessory muscles but remain at substantial risk of respiratory deterioration. The resulting respiratory failure may be hypoxemic, hypercapnic, or mixed in origin (40–42).

5. Motor and sensory disorders

Transverse SCI: complete and incomplete deficits

The transverse SCI produces clinical deficits that reflect the degree of disruption of ascending sensory and descending motor pathways. Rather than representing strictly separate categories, complete and incomplete injuries are better understood as points along a spectrum of transverse myelopathy, determined by the amount of preserved motor, sensory, and autonomic function below the neurological level of injury. A complete lesion is marked by the absence of motor and sensory function in all segments caudal to the injury, including the sacral segments S4–S5. In contrast, incomplete injuries retain some neural conduction through spared pathways, most notably demonstrated by sacral sparing. In the acute phase, this categorization may be complicated by spinal shock, a transient suppression of spinal reflexes resulting from the sudden loss of supraspinal inputs.

Spinal cord syndromes

Traumatic forces may selectively affect certain white matter pathways, leading to distinct clinical syndromes that can help identify the anatomical level and pattern of SC involvement (43–45).

- **Hemi-cord/Brown-Séquard syndrome:** it represents about 2-4% of SCI and results from a hemi-section of the SC producing a marked asymmetrical neurological deficit. Clinically, it manifests as an ipsilateral loss of motor function and proprioception due to involvement of the corticospinal tract and dorsal columns, associated with a contralateral loss of pain and temperature perception approximately one to two segments below the level of the lesion because of spinothalamic tract disruption.
- **Central cord syndrome:** the mechanism of the injury was originally proposed by Richard C. Schneider and colleagues, who suggested that it results from compressive forces generated during a cervical hyperextension, particularly in individuals with pre-existing spinal canal narrowing due to spondylotic degeneration. Clinically, it occurs with disproportionate upper extremity weakness, variable sensory loss and often better preservation of lower limb strength. Usually, the recovery takes place in a distal-proximal pattern.
- **Anterior cord syndrome:** it was described for the first time by William G. Spiller, and it is caused by the occlusion of the anterior spinal artery. This syndrome lead to bilateral motor paralysis, loss of pain and temperature at and below the injury level, while vibratory sensations and proprioception are spared. Prognosis is the worst between the incomplete SCI with a rate of motor recovery of 39%, remarking the vulnerability of the spinothalamic and corticospinal tracts to ischemia.
- **Posterior cord syndrome:** it is uncommon in trauma, but it is most common in syphilitic tabes dorsalis, multiple sclerosis, vascular malformations and spondylosis. This syndrome is characterized by loss of vibration and proprioception, while pain, temperature sensations and motor function are retained.

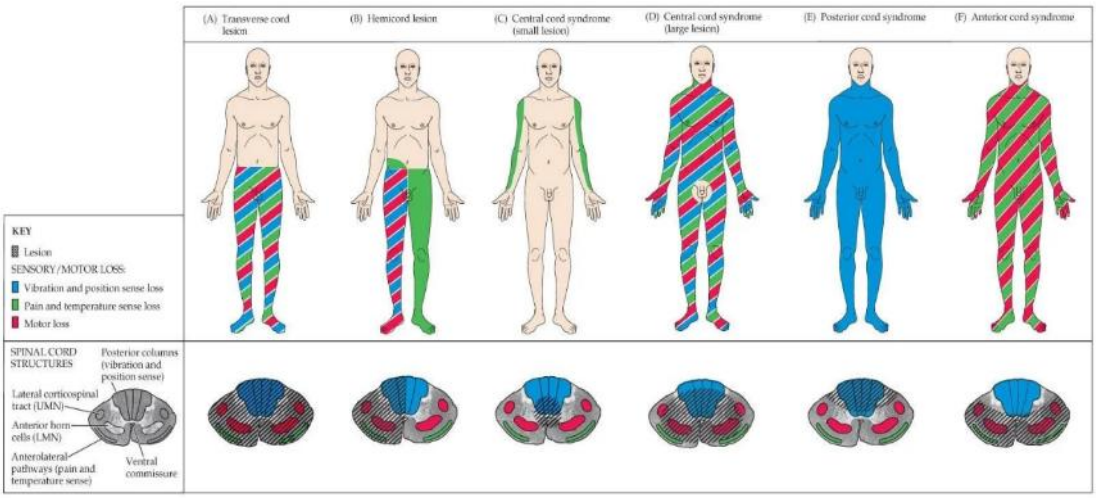


Figure 14: Overview on the spinal cord syndrome.
Source: https://www.maimonidesem.org/

1.4.4 Diagnosis and clinical evaluation

Initial clinical assessment includes a basic neurological examination, with a focus to the mechanism of injury and any loss of consciousness. In conscious patients, motor and sensory functions should be evaluated in detail. However, in polytraumatized patients, particularly when sedation or intubation is required, this assessment may be limited. In such cases, management should proceed under the assumption that a vertebral or SC injury may be present until proven otherwise (39,42).

ASIA Impairment Scale

The neurological examination is crucial, and it must include a meticulous evaluation of both motor and sensory functions, as well as the assessment of sacral nerve root integrity by evaluating rectal tone and tactile sensation within S4-S5 dermatomes or sensation to deep anal pressure. Sensory assessment involves the examination of 28 dermatomes on each side of the body. For each dermatome, pain sensation (pinprick) and light touch are evaluated and graded on a three-point scale (0 = absent, 1 = impaired, 2 = normal). Motor evaluation includes testing five key muscle groups in both the upper and lower extremities with strength graded from 0 to 5 according to the Medical Research Council (MRC) scale. In the upper limbs, the assessed functions correspond to elbow flexion (C5), wrist extension (C6), elbow extension (C7), finger flexion (C8), and little finger abduction (T1). In the lower limbs, the tested movements concern hip flexion (L2), knee extension (L3), ankle dorsiflexion (L4), great toe extension (L5), and ankle plantar flexion (S1). Traumatic SCI can be graded through the ASIA Impairment Scale which provides a standardized framework to classify SCI severity and discriminating complete from incomplete lesions (39).

Grade	Injury type	Features
A	Complete	No sensory or motor function is preserved in the sacral segment S4-S5
B	Incomplete	Sensory but not motor function is preserved at the most caudal sacral segments S4-S5 **AND** no motor function is preserved more than three levels below the motor level on either side of the body
C	Incomplete	Motor function is preserved at the most caudal sacral segments for voluntary anal contraction (VAC) **OR** the patient meets criteria for sensory incomplete injury (sensory function preserved at S4–S5 by LT, PP or DAP) and has motor function preserved more than three levels below the lesion. Less than half of muscles below the level of injury have a strength grade ≥ 3
D	Incomplete	≥50% of muscles below the level of injury have strength grade ≥ 3
E	None	Motor and sensory function are normal

Table 3: The ASIA Impairment Scale

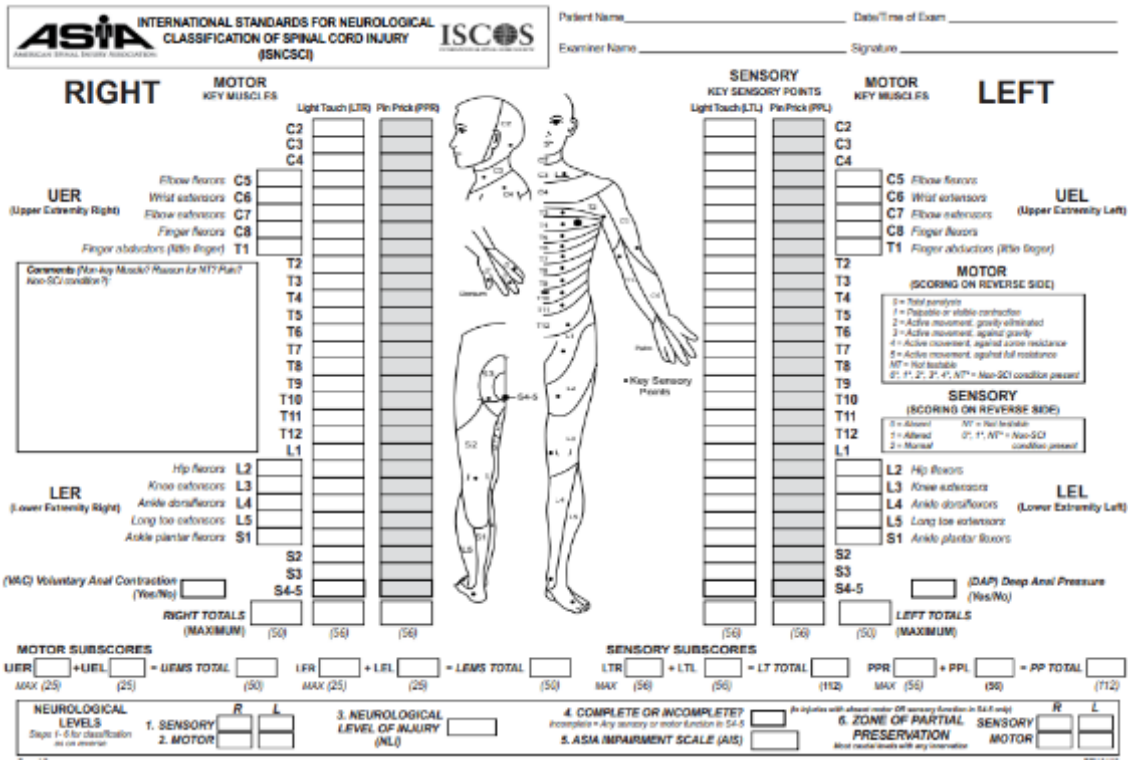


Figure 15: ASIA Impairment Scale Worksheet.
Source: https://asia-spinalinjury.org/

A key element in the evaluation of transverse SCI is determining whether sacral sparing is present, as this feature distinguishes complete (AIS A) from incomplete lesions (AIS B-D). Sacral sparing is defined by the preservation of any neurological function in the sacral segments S4–S5, including light-touch (LT), pin-prick sensation (PP), perception of deep anal pressure (DAP), or the ability to perform voluntary anal contraction (VAC). The preservation of even a single sacral function is sufficient to categorize the lesion as incomplete, regardless of the severity of neurological deficits above the sacral segments. In cases where sacral sparing is not present, the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) recommends probing the Zone of Partial Preservation (ZPP). This latter indicates the most caudal spinal segments below the neurological level of injury in which any residual motor or sensory function can still be detected, thereby providing a more accurate description of the inferior extent of the neurological deficit. In addition, the identification of ZPPs has relevant prognostic value, as preserved function within these segments is associated with a greater likelihood of neurological recovery, particularly regarding lower limb function. The 2019 revision of the ISNCSCI expanded the use of ZPPs, allowing them to be recorded not only in complete injuries, but also in certain incomplete injuries in which sacral motor or sensory function is absent, thus increasing the descriptive precision and prognostic utility of the classification system (39,46).

Radiologic assessment

Combined with the neurological examination, the radiologic assessment should be performed promptly after the trauma, as it plays a crucial role in guiding subsequent clinical decision-making. In awake trauma patients, cervical spine imaging may be safely omitted when specific clinical criteria are fulfilled. In the absence of neck pain or tenderness, with a normal neurological examination, preserved cervical range of motion (ROM) and absence of painful injury causing distraction the likelihood of a clinically significant cervical SCI is extremely low. Under these conditions, radiological evaluation is generally not indicated. Magnetic resonance imaging (MRI) and computed tomography (CT) now play a central role in the early assessment of SCI. CT provides characterization of vertebral fractures, although it remains limited in detecting soft tissue damages. Instead, MRI allows detailed visualization of soft tissues and can detect ligamentous damage, disc herniation, epidural hematoma, as well as intramedullary oedema or haemorrhage that may not be evident on CT scans. These findings directly influence decisions regarding stability and surgical planning. Current practice supports obtaining an MRI within 24 hours in situations where spinal stability is uncertain and may alter surgical indications, neurological deficits are not explained by CT findings and eventually when progressive or unexplained clinical deterioration is observed (47,48).

1.4.5 Acute treatment of SCI

Pre-hospital care and immobilization

The identification or suspicion of SCI, together with safe transport to hospital, represent the initial step in appropriate patient management. In life-threatening situations, the patient should be stabilized and transferred to the nearest hospital, with subsequent referral to a specialized SCI center as soon as possible, ideally within the first 24 hours. The first assessment is carried out on the accident site following the ABCDE (Airways, Breathing, Circulation, Disability, Exposure). Subsequently, a neurological examination is performed with evaluation of the 4 extremities to investigate the presence or absence of SCI. Lastly, it is essential to identify the individuals who require spinal immobilization and apply appropriate stabilization measures. When vertebral injury is suspected, immobilization of the entire spinal column is recommended observing the National Emergency X-Radiography Utilization Study (NEXUS) and the Canadian C-Spine Rule (CCSR) criteria, as approximately 20% of patients may present additional non-contiguous vertebral lesions (49,50).

Cardiovascular management

The main procedure in cardiovascular management is the increase in blood pressure, since arterial hypotension is associated with a worse prognosis due to inadequate perfusion and the perpetuation of the secondary damage. Maintaining the mean arterial pressure (MAP) within a target range of 85–90 mmHg for at least seven days, achieved through appropriate fluid management and the use of vasopressors, has been associated with improved clinical outcomes (41,51,52).

Respiratory management

The severity of respiratory failure is closely related to the height of the lesion. Routine interventions, such as respiratory physiotherapy and secretion suctioning are beneficial in increasing airway compliance and clearance. Continuous monitoring in patients with cervical SCI is mandatory. If the lesion is above C5, therefore affecting the functionality of the diaphragm (C3-C4) and the patient has complete quadriplegia, intubation is necessary in 95% of cases (53). Furthermore, in individuals with reduced motor function, according to the AIS, and persistent respiratory compromise, tracheostomy should be performed to reduce the morbidity and improve long-term respiratory management (54). Finally, recent studies suggest that diaphragmatic pacing may significantly optimise spontaneous breathing in selected patients. This intervention can promote greater respiratory autonomy and, in some cases, allow individuals to achieve partial or complete independence from mechanical ventilation (41,55).

Surgical management

The main goal of surgery is to decompress and stabilize the spine thus eliminating the source of secondary injuries and enhancing neurological recovery. However, the optimal timing of surgical intervention remains a matter of debate, current evidence suggests potential benefits of early treatment. In particular, the STASCIS (Surgical Treatment in Acute Spinal Cord Injury Study) showed that in patients undergoing decompression in the first 24 hours after the accident there was an improvement of at least 2 points in the AIS scores. The choice of surgical approach depends largely on the underlying pathology and the site of compression. For instance, an SCI caused by an anteriorly displaced cervical disc requires an anterior approach; conversely, a patient with central cord syndrome due to multi-level compression is managed with a posterior approach (56,57).

Neuroprotection

Neuroprotective strategies aim to mitigate secondary injury mechanisms by reducing inflammation and promoting tissue repair. The use of corticosteroids remains controversial, and it is generally reserved for highly selected cases. According to the Cochrane Review, high-dose methylprednisolone may provide modest neurological improvement when administered within 8 hours of traumatic SCI and only in patients without significant contraindications. Although, the use of steroids is related to several complications such as wound infection, pneumonia, sepsis, acute respiratory distress syndrome and gastrointestinal bleeding (58,59). Therapeutic hypothermia has also been investigated as a neuroprotective strategy, as it may exert beneficial effects through metabolic suppression, particularly during ischemic phases (60). Finally, riluzole (glutamate antagonist) has emerged as a potential neuroprotective agent for his ability to reduce excitotoxicity and neuronal apoptosis (61).

1.5 Neurological sequelae

The SCIs frequently result in neurological impairment below the level of the lesion, affecting both motor and sensory pathways and leading to significant functional limitations that impact mobility, independence in activities of daily living, and overall quality of life (QOL). The neurological severity of SCI is typically classified using the ASIA Impairment Scale, which provides standardized criteria for determining the neurological level and completeness of injury (62). As discussed in the previous chapter, this classification system represents the reference framework for the neurological assessment of patients with SCI and plays a crucial role in prognosis, clinical management, and research.

1.5.1 Motor deficits

1.5.1.1 Definition

The motor impairments arise from disruption of descending pathways, particularly the corticospinal tract, resulting in reduced or absent voluntary muscle activation below the injury level (2,3). The extent and distribution of motor deficits depend mainly on the neurological level of injury and the completeness of the lesions; when they are located at the higher spinal levels generally produce more extensive motor impairment, because a greater number of spinal segments and corresponding muscle groups are affected.

1.5.1.2 Pathophysiology

An immediate consequence of SCI is the disruption of the ascending and descending pathways with a consequent axonal damage combined with scarring and infiltration of fibrotic cells that generate a permanently disorganized ECM (63,64). Motor deficits derive from interruption of pyramidal (especially the corticospinal tract) and extrapyramidal (vestibulospinal, reticulospinal, rubrospinal, olivospinal tracts) pathways giving raise to muscular paralysis. However, the motor dysfunction is not only related injury of the corticospinal tract but may also result from direct damage to secondary motor neurons (65). Moreover, the loss of supraspinal input can lead to transsynaptic degeneration of these neurons, further contributing to motor impairment (66). Following SCI, the skeletal muscle undergoes a series of morphological and functional changes. First, a reduction in the number of motor units (MUs) has been demonstrated through Motor Unit Number Estimation (MUNE), which has been assessed in several studies, particularly in the tibialis anterior and abductor hallucis muscles, consistently reporting a decline (67,68). Secondarily, an alteration in the strength produced by MUs occur; these changes are influenced by factors such as disuse-related muscle atrophy, varying degrees of compensatory motor axonal sprouting toward the MU, and the specific types of MUs that are spared (69,70). Furthermore,

impairments in firing rate and increased recruitment threshold contribute to the reduction in muscular strength. Finally, studies have reported a progressive increase in the H-reflex and in the H-reflex/Mmax ratio after SCI, suggesting reduced presynaptic inhibition and consequent alterations in motor neuron excitability (71–74).

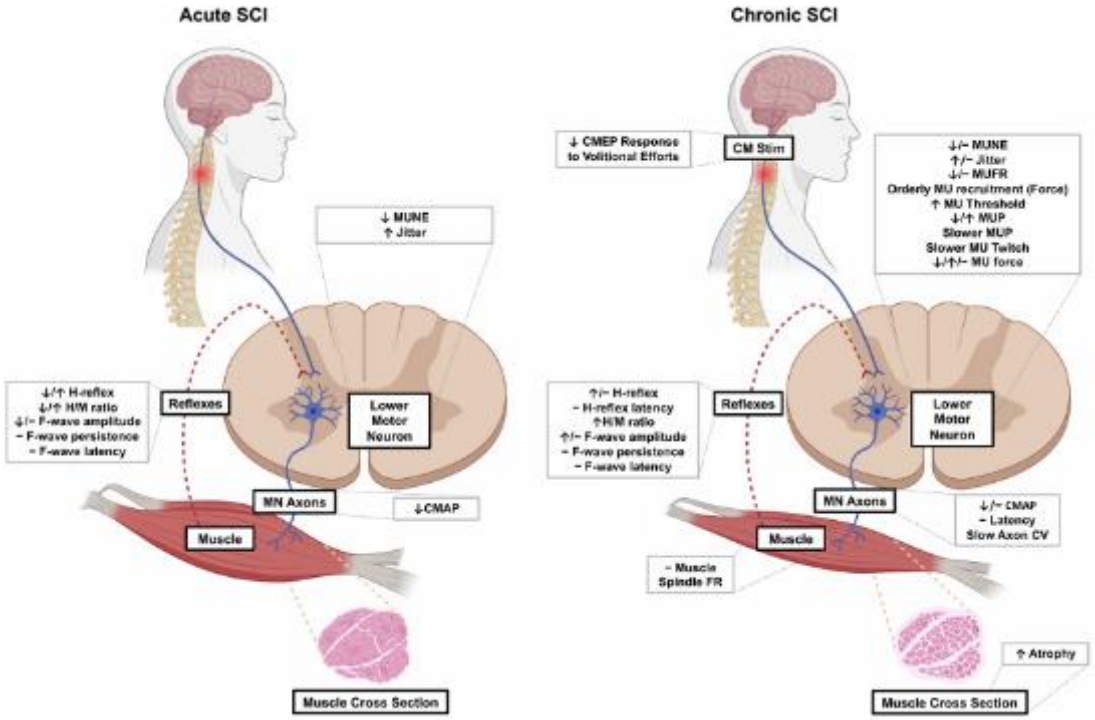


Figure 16: Conceptual model of how subacute (less than 1 year) and chronic can influence lower motor neuron excitability, motor unit properties, and motor unit number estimates (MUNE).
The blue lines represent the efferent signal while the red lines depict the afferent signal. Grey boxes describe the adaptations resulting from SCI to each neuromuscular component and integration site.
CM Stim=cervico-medullary stimulation; CMAP= compound muscle action potential; CMEP= cervico-medullary evoked potential; CV= conduction velocity; FR= firing rate; MN= motor neuron; MU= motor unit; MUP= motor unit potential.
Source: Debenham, M. I. B., Franz, C. K., & Berger, M. J. (2024). Neuromuscular consequences of spinal cord injury: New mechanistic insights and clinical considerations. Muscle & nerve, 70(1), 12–27.

1.5.1.3 Clinical presentation

Depending on the time phase of SCI, motor symptoms vary. In the spinal shock phase, between 0 and 24 hours, the patient experiences hyporeflexia or even areflexia. In the late phase, however, between 1 and 12 months, following the growth of axons and the creation of new synapses, cutaneous and deep tendon reflexes will be hyperactive even with minimal stimuli (72,75). Clinically, these impairments range from paresis to plegia. The first one refers to a partial deficit of muscle strength with some preservation of the ability to activate the muscles, while the last is defined as a complete loss of voluntary motor function. Based on the anatomical level of the lesion, different clinical pattern may occur: cervical injuries, generally, result in tetraplegia or

tetraparesis, involving both upper and lower limbs. Conversely, thoracic, lumbar, or sacral injuries more commonly lead to paraplegia or paraparesis, primarily affecting the lower limbs with preservation of upper limb function (62).

1.5.1.4 Evaluation

In order to assess the degree of recovery after SCI, it is necessary to employ valid and standardized measures of functional and neurological outcome. During the evaluation two parameters are commonly considered: ambulatory capacity and ambulatory performance. Within this framework, ambulatory capacity refers to the highest level of walking ability that an individual can achieve under standardized or controlled conditions. In contrast, ambulatory performance describes the level of walking activity that the individual demonstrates in everyday environments (76,77). The main criteria used will be discussed below.

Clinical outcomes measures

1.The 10-Meter Walk Test (10MWT)

The 10MWT is used to assess walking ability by recording the time required to cover a distance of 10 meters; it may be performed with physical assistance or with the use of assistive ambulation devices when necessary, allowing the calculation of walking speed. The test can be administered under either static or dynamic start conditions (78,79). Given the strong correlation and overlap between the results of the two approaches, gait speed in the 10MWT may also be calculated using the static method (80).

2.The 6-Minutes Walking Test (6MWT)

The 6MWT is employed to measure walking ability and endurance. It represents an adaptation of the original Twelve Minute Walking Test. During this test, the participant is instructed to walk for six minutes along a straight indoor corridor at least 30 meters long, while the total distance travelled by the patient is recorded. The test should be administered twice, with a one-hour interval between trials, and the best result is considered for analysis (78,79,81).

3.The Timed Up and Go Test (TUGT)

The TUGT involve standing up from a seated position, walking three meters, turning around a marker and then sitting down in the chair quickly and safely as possible. The total time required is recorded. This measure provides information about the individual's balance, walking ability, postural control and risk of fall (82).

4.The Walking Index for Spinal Cord Injury II (WISCI)

Unlike the previously described tests, the WISCI II was specifically developed for individuals with SCI rather than being adapted from other populations. Instead of measuring walking performance, it evaluates the level of assistance required for ambulation (79). During the assessment, the patient is asked to walk 10 meters while the examiner observes the need for braces, assistive devices, or physical assistance. Based on these factors, a score ranging from 0 to 20 is assigned, with lower scores indicating a higher impairment.

5.Muscle strength assessment

Assessment of muscle strength represents a fundamental step in the evaluation, as it helps determine the severity of the impairment and the planning of appropriate rehabilitation strategies. The American Spinal Injury Association (ASIA) recommends evaluating muscle strength through the Manual Muscle Test (MMT) (83). However, Schwartz and colleagues demonstrated that this method has limited accuracy, as different levels of muscle strength may exist within the same MMT grade (84). This finding suggests that improvements resulting from therapeutic interventions, missed by the MMT, could instead be detected using a handheld myometer. For this reason, the use of myometric measurements has been proposed as a more precise approach for quantifying muscular strength.

Neurophysiological outcome measures

1.Electromyography (EMG)

The EMG can be used to monitor SCI progression by analysing both time and frequency domain variations (85). Electromyographic patterns reflect different disease stages: during spinal shock, surface EMG (sEMG) amplitude is reduced, gradually increasing over four weeks and reaching a plateau around 22^{nd} week (86). Studies have shown a correlation between sEMG and muscle strength after SCI, with patients exhibiting markedly reduced activation during maximal voluntary contractions, approximately 71% of muscles generate less than 10% of the activity observed in healthy controls (87,88). Despite its potential, sEMG is not widely adopted clinically due to limited clinician training and confidence, variable signals in subjects with SCI, and the absence of standardized protocols (89).

2.Motor Evoked Potentials (MEPs)

The MEPs monitor the integrity of the motor pathways, particularly the corticospinal tract, in a non-invasive manner. It involves applying transcranial magnetic stimulation while recording the

peripheral responses of muscle groups. It has been proven that MEPs can provide predictive information regarding motor recovery and ambulatory capacity during follow-up of patients with SCI, particularly when used in combination with the ASIA Impairment Scale. In fact, these individuals commonly demonstrate MEP abnormalities, including reduced amplitudes, prolonged latencies, or absent responses (90,91).

1.5.1.5 Treatment

The management and treatment of motor deficits after a SCI are based on a multidisciplinary approach aimed at maximizing functional recovery, promoting neuroplasticity, and improving QOL. Current strategies encompass a range of interventions, including rehabilitation therapies, pharmacological treatments, and neuromodulation techniques.

Rehabilitation

The main purposes of physical rehabilitation are to restore functional ambulation and prevent complications. It focuses on strength training, cardiovascular exercise, respiratory conditioning, mobility training, and stretching for avoiding muscle spasms (92). Currently, the rehabilitation program can be carried out using various techniques (93,94).

- **Body Weight Support on a Treadmill Training (BWSTT):** allows patients with limited motor control to practice stepping movements in a safe and controlled setting while a harness system partially unloads body weight. During training, therapists may provide manual assistance to facilitate appropriate limb kinematics and trunk stabilization (95).
- **Overground walking training:** it is typically introduced when the patient can stand independently while supporting at least 80% of their body weight and can initiate stepping with at least one lower limb**.** When additional support is required, balance may be facilitated by physical therapists or with assistive devices such as side rails or canes (95).
- **Robotic Assisted Gait Training (RAGT):** it encompasses devices that are designed to facilitate gait rehabilitation while reducing the physical demands for both patients and therapists. They can be employed in a variety of settings, including both indoor and outdoor environments (96). However, their use often requires substantial upper-limb effort and adequate muscle strength. Several studies have reported that these technologies can contribute to improvements in mobility and may also help reduce spasticity and pain (97,98).

Nevertheless, to date, there is still insufficient evidence to determine which physical therapy approach is best for recovery from SCI impairments (99).

Figure 17: Motor devices for Robotic Assisted Gait Training (RAGT).
Source: Behrman, A. L., & Harkema, S. J. (2000). Locomotor training after human spinal cord injury: a series of case studies. Physical therapy, 80(7), 688–700.

Functional electrical stimulation (FES)

Functional electrical stimulation (FES) is a device that uses electrical current to elicit a response in excitable cells. Particularly, it is used to activate muscles according to a specific temporal and spatial pattern, thereby producing the movements that support functional tasks (92). The system typically consists of a stimulator that delivers electrical pulses trough electrodes, which may be implantable, percutaneous, or surface-mounted (100). Its clinical application ranges from the restoration of upper and lower limb function, especially hand grasp and locomotion, as well as improvements in trunk stability and bladder control (94,101). In gait rehabilitation, several devices have been developed, such as the one introduced by Kralj (102), the Parastep neuroprosthesis (103), the Reciprocating Gait Orthosis (RGO) and hybrid FES systems that combine electrical stimulation with orthotic components (104,105).

Spinal Cord Stimulation (SCS)

Spinal Cord Stimulation (SCS) has emerged as a promising approach for promoting motor recovery in individuals with SCI. This technique involves the implantation of electrodes in the

epidural space to modulate spinal motor circuits and facilitate the recovery of coordinated motor activity (106). Integrating this technology with physical rehabilitation may enhance functional outcomes and support the restoration of motor function (107). A detailed discussion of Spinal Cord Stimulation (SCS) is provided in Chapter 1.7.

1.5.2 Sensory deficits

1.5.2.1 Definition

Sensory deficits result from damage to the ascending pathways of the SC, which transmit somatosensory information from peripheral receptors to the brain. These pathways convey different types of input, including light touch, proprioception, vibration, pain, and temperature. Subsequently to the SCI, the interruption or degeneration of these neural structures leads to partial or complete loss of sensation below the level of the lesion (2,3).

1.5.2.2 Pathophysiology

The initial mechanical trauma to the SC causes a disruption and displacement of the vertebral columns, which may determine a compression or a transection of SC. This damage affects both ascending and descending pathways. Following the primary injury, the death of neurons and glial cells occur leading to demyelination and progressive loss of neural circuits (63,92). The pattern of sensory deficits reflects the differential involvement of ascending pathways and their specific functional roles in sensory transmission: this phenomenon is called sensory dissociation. Damage to the dorsal columns (gracile and cuneate tracts) results in the loss of discriminative touch, vibration sense, and conscious proprioception. Interruption of the anterolateral system, particularly the spinothalamic tract, causes loss of pain, temperature, and non-discriminative touch (43,44). Finally, damage to the dorsal and ventral spinocerebellar tracts compromises unconscious proprioception, leading to alterations in automatic coordination of movement and balance, even in the presence of relatively preserved conscious sensation (2). As emphasized by Serge Rossignol and colleagues, locomotion depends on dynamic interactions between spinal motor circuits and sensory feedback originating from muscles, joints, and cutaneous receptors. After SCI, disruption of these afferent signals compromises the normal sensory-motor integration, contributing to impairments in locomotion, balance, and coordinated movement (108).

1.5.2.3 Clinical presentation

Following a SCI, changes in somatosensory perception can occur in terms of both quantity and quality of the sensory experience. The clinical presentation varies according to the level and extent of the lesion and may include both loss of normal sensation and the emergence of abnormal sensory phenomena (15).

Quantitative sensory alterations

Quantitative sensory deficits are characterized by a reduction or complete absence of sensory perception below the neurological level of injury (39). These deficits may manifest as:

- **Anaesthesia:** complete loss of sensory perception, including tactile, thermal, and nociceptive sensations below the level of injury. This condition is typically observed in clinically complete injuries.
- **Hypoesthesia:** partial reduction in sensory perception. It is more commonly associated with incomplete injuries, where sensory function is preserved but diminished or uneven.

Qualitative sensory alterations

In addition to the loss of normal sensation, individuals with SCI frequently experience qualitative sensory disturbances resulting from altered sensory processing and CNS reorganization. These include:

- **Paresthesias**: spontaneous, non-painful sensations such as tingling, pins-and-needles, or electric-shock-like feelings perceived in the absence of an external stimulus.
- **Dysesthesias:** abnormal and unpleasant sensations, spontaneous or evoked, often described as burning or discomfort.
- **Pain-related sensory disturbances:** such as allodynia and hyperalgesia, characterized respectively by pain elicited by normally non-painful stimuli and by an exaggerated response to painful stimuli.

These abnormal sensory experiences may also occur in patients who appear to have no conscious sensation during standard neurological examination and have also been described in individuals with clinically complete injuries, suggesting the presence of residual sensory transmission that cannot be detected by conventional assessments, a condition defined as “sensory incomplete spinal cord injury” (109,110).

1.5.2.4 Evaluation

A variety of clinical and instrumental methods have been developed to assess sensory function, each providing complementary information on the integrity of the somatosensory system.

Somatosensory Evoked Potentials (SEPs)

The Somatosensory Evoked Potentials (SEPs) constitute a non-invasive technique for assessing the integrity of the SC and sensory pathways. Low electrical stimuli are applied to any point of sensory organ, sensory nerve or sensory pathways, and the cortical response is recorded through surface electrodes placed on the scalp at the level of the primary sensory area in the parietal lobe.

In SCIs only the damage to the posterior columns causes morphological changes, extending of latency, or abolition of SEPs (111). Numerous subsequent studies have shown that SEPs can be correlated with patient locomotor outcomes, as they are strongly correlated with the ASIA score. Furthermore, SEPs are not affected by spinal shock; consequently, they can be used as a highly sensitive tool for the follow-up (39,112–114).

Quantitative Sensory Testing (QST)

The Quantitative Sensory Testing (QST) represents an important tool to assess the sensory function, including in case of SCIs. During this test, patients are exposed to standardized and quantifiable sensory stimuli and based on his feedback perception thresholds are identified for the light touch, pressure, vibration, thermal sensations, heat and cold pain. These measurements allow clinicians to identify the detection threshold of the patient and, when abnormalities are present, to infer possible damage to the sensory pathways (115). Previous studies have shown that the individuals with SCI exhibit different perceptual threshold values for warm, cold and vibratory sensations (116). Overall, The QST will help to characterize the different somatosensory phenotypes due to the spinal lesions.

Proprioception assessment

Proprioceptive function can be assessed using various tools, including dynamometers and force platforms. The dynamometers quantify the joint position sense and the movement detection thresholds by measuring the joint repositioning errors. In this test, a limb segment is moved to a predefined angle, and the participant is asked to reproduce the same position either actively or passively. The difference between the target angle and the reproduced angle represents the repositioning error and reflects the accuracy of proprioceptive perception (117,118). Force platforms, on the other hand, measure ground reaction forces and the displacement of the centre of pressure during standing or locomotor tasks (119). Analysis of these parameters provide indirect assessment of the integrity of sensorimotor pathways, and their changes are correlated with the patient's ambulatory outcome.

1.5.2.5 Treatment

Proprioceptive feedback plays a fundamental role in both the recovery and maintenance of locomotor function following SCI (120). Accordingly, targeted sensory rehabilitation is essential to refine the spinal networks, enhance their functional relevance, and ultimately improve motor outcomes. Among the available strategies, the AMES device (Assisted Movement with Enhanced Sensation) integrates assisted joint mobilization, proprioceptive stimulation, and real-time biofeedback. The system induces cyclic flexion and extension of the joint, during which the patient attempts to actively participate by promoting the movement. At the same time, vibration

is applied at the tendon level to enhance proprioceptive feedback (121). In parallel, neuromodulatory techniques such as epidural or transcutaneous electrical stimulation provide external inputs that engage residual spinal circuits and exploit intrinsic spinal automaticity (106,122). Collectively, these approaches contribute to the recovery of coordinated movement and functional motor performance by reinforcing the interaction between sensory input and motor output.

1.5.3 Autonomic dysfunctions

1.5.3.1 Definition

The autonomic nervous system plays an important role in maintaining homeostasis and providing control over multiple peripheral organ systems. Autonomic dysfunction represents a major and often underrecognized consequence of SCIs. Depending on the level and severity of the lesion, impairments may affect multiple organ systems, including cardiovascular, respiratory, thermoregulatory, gastrointestinal, and genitourinary functions. These disturbances can significantly influence the QOL, increasing the risk of medical complications (40).

1.5.3.2 Pathophysiology

Autonomic dysfunction following SCI arises from the disruption of descending pathways that modulate both sympathetic and parasympathetic activity. This damage results in a loss of inhibitory control and a greater reliance on spinal circuits, leading to exaggerated sympathetic reflex responses. Furthermore, following the SCI, the immune system is activated triggering plasticity phenomena. Although, maladaptive plasticity is also implicated in the onset of sympathetic hyperreflexia and associated peripheral organ damage. The severity of these alterations is strongly influenced by the level of the lesion. High-level injuries, particularly those above the upper thoracic segments, create a complete disconnection between preganglionic sympathetic neurons located in the thoracolumbar SC and the supraspinal control centers, giving rise to increase sympathetic reflexes that culminate in the dysfunction of peripheral organs. In contrast, lower-level SCI preserve a higher degree of supraspinal connectivity, thereby limiting the extent of autonomic disruption and reducing the severity of peripheral organ involvement (123).

1.5.3.3 Clinical presentation

Cardiovascular dysfunctions

The patients with SCIs have a high risk to develop the following cardiovascular complications (124).

- **Orthostatic Hypotension (OH):** it is defined as a decrease in systolic blood pressure of at least 20 mmHg or a reduction in diastolic blood pressure of at least 10 mmHg, when the body position changes from supine to a standing position. The OH occurs with dizziness, headache, sweating, pallor, muscle weakness and occasionally syncope. The mechanism underlying OH is characterized by a decrease in sympathetic outflow associated with a loss of the vasoconstriction reflex (123).
- **Autonomic Dysreflexia (AD):** it is caused by a stimulus below the lesion, such as bladder or bowel distension. This triggers a massive reflex response resulting in widespread vasoconstriction and acute hypertension. In response, there is a compensatory parasympathetic activity above the level of injury, leading to characteristic clinical manifestations such as headache, facial flushing, profuse sweating, and nasal congestion (125). Over time, the AD increases the patient's risk of stroke and myocardial infarction (126).
- **Arrhythmias:** these are generally cases of bradycardia (especially in the acute phase), and they are typical in subjects with high-level lesions (123).

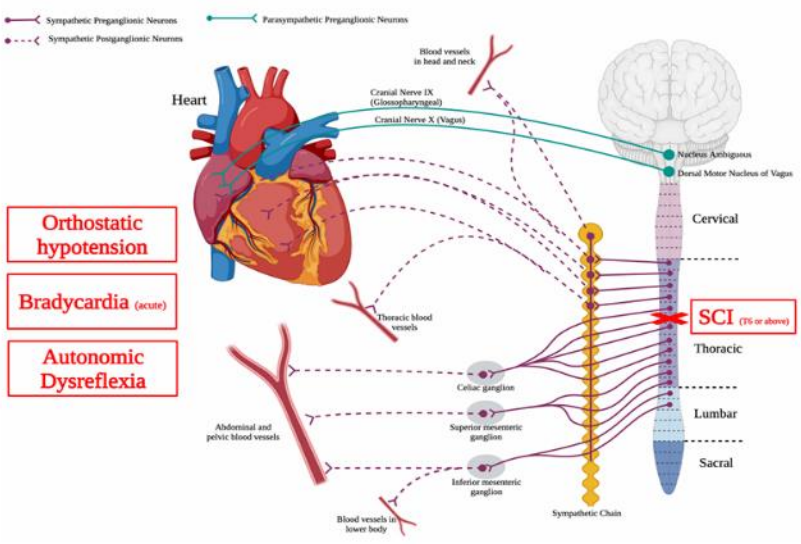


Figure 18: SCI at or above T6 results in deranged sympathetic activity causing orthostatic hypotension, bradycardia in the acute phase, and autonomic dysreflexia.
Source: Wulf, M. J., & Tom, V. J. (2023). Consequences of spinal cord injury on the sympathetic nervous system. Frontiers in cellular neuroscience, 17, 999253.

Respiratory dysfunctions

The PNS and SNS exert opposing effects on the airways: parasympathetic activation induces bronchial smooth muscle contraction, whereas sympathetic activity promotes bronchodilation. The injuries above the T5 level disrupts sympathetic outflow while largely preserving parasympathetic function, resulting in a consequent airway hyperreactivity, which may contribute to a higher incidence of asthma in this population (123,127). In addition, SCI is frequently associated with respiratory muscle weakness and spasticity, impairing cough effectiveness and reducing the ability to clear the airways from secretions and foreign materials. It has been shown that these alterations in the autonomic control of the respiratory system can predispose to the sleep-related breathing disorders (123,128).

Gastrointestinal dysfunctions

Certain parts of the gastrointestinal tract are controlled autonomously by the enteric nervous system (ENS). Although the ENS is autonomous, it is influenced by branches of the autonomic nervous system. In physiological conditions, parasympathetic input enhances digestion and promotes peristalsis, whereas sympathetic activity inhibits intestinal motility and increases anal sphincter tone. The disruption of this balance, caused by SCI, results in the neurogenic bowel. This is a fairly common complication affecting approximately 46.9% of individuals with SCI (129). Two types of neurogenic bowel have been identified (130):

- **The hyper-reflexic bowel syndrome:** it typically occurs when the lesions are above the *conus medullaris* and it is characterized by increased anal sphincter tone, resulting in constipation and faecal retention.
- **The areflexic bowel syndrome:** it arises from damage to the parasympathetic cell bodies located in the *conus medullaris*, *cauda equina*, or pelvic nerves. This form is associated with reduced sphincter tone and impaired control of the levator ani muscle, leading to constipation accompanied by a significant risk of faecal incontinence

The neurogenic bowel is also associated with alterations of intestinal microbiota, in fact emerging evidence suggest that this dysbiosis can contribute to the development of gastrointestinal disorders, such as irritable bowel syndrome and chronic bowel diseases (123,124,131).

Urological dysfunctions

Physiologically, as the bladder fills, the detrusor muscle relaxes while the urethral sphincter contracts. Specifically, sympathetic activity facilitates urine storage, whereas parasympathetic activation promotes bladder emptying. Following SCIs, this mechanism is impaired leading to neurogenic bladder, which represents a very common complication in this type of patients. This

condition is associated with an increased risk of urinary tract infections. Depending on the level of the injury, there will be different clinical presentations of neurogenic bladder:

- **UMN injury:** it leads to the development of spastic bladder, often accompanied by detrusor–sphincter dyssynergia (DSD), a condition in which the detrusor muscle and urethral sphincter contract abnormally simultaneously, thereby impairing effective bladder voiding.
- **LMN injury:** it results in flaccid bladder characterized by the absence of detrusor contraction, thereby causing urinary retention associated with progressive bladder overdistension.

Furthermore, patients with SCI are at higher risk of developing nephrolithiasis (123,124).

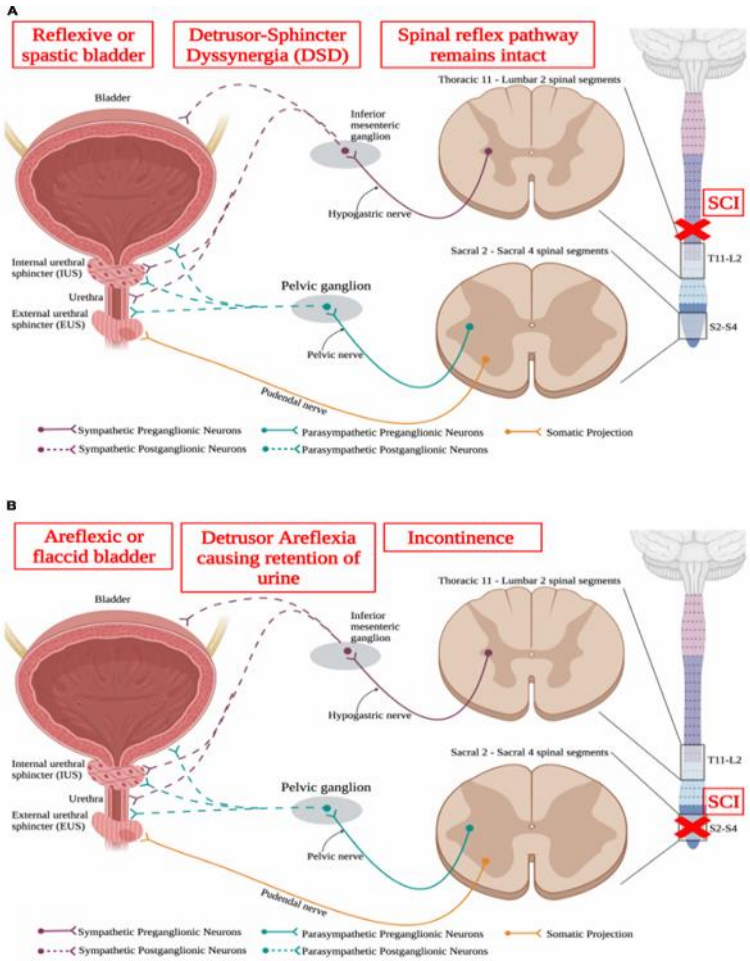


Figure 19: bladder dysfunction after SCI.
***A)** The Upper Motor Neuron (UMN) injury.*
***B)** The Lower Motor Neuron (LMN) injury.*
Source: Wulf, M. J., & Tom, V. J. (2023). Consequences of spinal cord injury on the sympathetic nervous system. Frontiers in cellular neuroscience, 17, 999253.

Thermoregulatory dysfunctions

People with SCI, particularly those with high thoracic or cervical lesions, often exhibit impaired thermoregulation and may behave in a poikilothermic manner, meaning that their core body temperature tends to fluctuate with the surrounding environment. Under physiological conditions, thermoregulation is coordinated by the preoptic area of the hypothalamus and the thalamus, which integrate afferent input from peripheral thermal receptors and activate autonomic responses such as vasodilation, sweating, and modulation of heat exchange through radiation, convection, conduction, and evaporation. The disruption of sympathetic pathways below the level of injury limits the ability to redistribute warm blood to the skin and impairs sweating: as a result, heat dissipation becomes inefficient, while compensatory flushing and excessive sweating may occur above the level of injury. This autonomic dysfunction predisposes individuals to neurogenic fever, defined as a body temperature exceeding 37.7 °C, which is considered a diagnosis of exclusion after ruling out other causes such as infection, thromboembolism, or drug-related fever. Impaired thermoregulation also increases the risk of exercise-induced hyperthermia and, conversely, hypothermia in cold environments due to altered counter current heat exchange mechanisms (40,132).

Sexual dysfunctions

Sexual and reproductive functions are regulated through the integrated activity of the autonomic and somatic nervous system. The SCIs frequently disrupt these pathways, resulting in sexual dysfunction, that can significantly affect psychological well-being. In males, the SNS has an anti-erectile effect, whereas the PNS has a pro-erectile effect. During ejaculation, the SNS plays a key role in the phase of semen emission, while the PNS facilitates the phase of semen expulsion. The SCIs interfere with these coordinated mechanisms, often leading to erectile dysfunction and abnormal ejaculation, which in turn contribute to low fertility rates in these individuals. In females, the PNS plays a key role in clitoral erection and vaginal lubrication while SNS is involved in sexual arousal. Following a SCI, difficulties in achieving physical and psychological arousal along with a reduction in vaginal lubrication have been reported, particularly for injuries above T12. Despite these impairments, menstrual function is generally preserved, and many women retain the ability to conceive and carry a pregnancy to term (123).

1.5.3.4 Evaluation

Currently, the assessment of autonomic functions following a SCI is inadequate. The complexity of the autonomic nervous system and its regulatory role in almost all the body's organs make it difficult to develop and select appropriate tests for post-injury assessment. For a systematic and reproducible evaluation, the International Standards to document Autonomic Function after

Spinal Cord Injury (ISAFSCI) are recommended, as they provide a standardized framework for classifying residual autonomic function across the cardiovascular, sudomotor, genitourinary, bronchopulmonary and reproductive systems (133,134). From a cardiovascular perspective, measuring blood pressure and heart rate at rest and during orthostatic stress, along with the tilt table test and heart rate variability (HRV) analysis, allow for the diagnosis of OH and AD (135). Sudomotor and thermoregulatory function can be assessed using sweating tests, such as the Quantitative Sudomotor Axon Reflex Test (QSART) or the thermoregulatory sweat test, which reveal loss of sympathetic innervation below the level of the lesion (136). Bladder and bowel autonomic function assessment involves urodynamic studies, anorectal function tests and the Neurogenic Bowel Dysfunction (NBD) score calculation (137,138). The combined use of physiological tests and standardized scores offer a comprehensive characterization of autonomic deficits, which is useful for both clinical monitoring and for research and prognostic stratification.

1.5.3.5 Treatment

The management and treatment of autonomic disorders resulting from the lesion require an approach based on non-pharmacological strategies, pharmacological interventions, and neuromodulatory techniques.

Non-pharmacological management

Non-pharmacological management is the first line of treatment and consists primarily of trigger prevention and patient education. Key strategies include careful management of the bladder emptying through intermittent catheterization, bowel management with a high-fiber diet, abdominal massage and routine monitoring of skin integrity to prevent pressure ulcers. Concerning the OH gradual postural mobilization, the use of compression stockings or abdominal binders, adequate hydration, and a controlled increase in sodium intake are recommended. In cases of autonomic dysreflexia, prompt recognition of symptoms and rapid removal of the triggering stimulus are essential (123,124).

Pharmacological treatment

When conservative measures prove insufficient, it is recommended to switch to pharmacological treatment. The OH, is commonly managed with vasopressor agents such as midodrine and, in selected cases, fludrocortisone in order to increase vascular tone and intravascular volume. In contrast, acute autonomic dysreflexia requires treatment with fast-acting antihypertensive drugs, such as nitrates, nifedipine, or captopril, aimed at reducing the risk of cerebrovascular and cardiac complications. Bowel dysfunction is typically treated with stool softeners, bulk-forming agents, and colonic stimulants to facilitate regular evacuation. Finally, the pharmacological measures for

neurogenic bladder involve the use of anticholinergic medications, α-blockers, and intra-detrusor injections of botulinum toxin to improve bladder storage and emptying function (123,124,137).

Neuromodulation

In recent years, both transcutaneous and epidural spinal cord stimulation have demonstrated promising results in modulating cardiovascular function, improving blood pressure stability. Moreover, these approaches have shown potential in bladder control by engaging residual spinal circuits and in the management of neurogenic bowel, likely by increasing external anal sphincter and pelvic floor muscle tone (106,123,139,140).

1.5.4 Spasticity

1.5.4.1 Definition

Spasticity is one of the most emblematic and yet misunderstood consequences of upper motor neuron damage following SCI. Traditionally, according to Lance, it has been defined as a motor disorder characterized by a velocity dependent increase in muscle tone associated with exaggerated tendon reflexes, resulting from hyperexcitability of the stretch reflex (141). However, contemporary neurophysiology recognizes spasticity as a more complex phenomenon, arising from widespread reorganization of spinal networks after the loss of supraspinal control. To address these issues, the European working group EUSPASM proposed a revised definition of spasticity as a disorder of sensorimotor control characterized by intermittent or sustained involuntary muscle activation (142). The literature has shown that 65–78% of individuals with chronic SCI (>1 year) exhibit symptoms of spasticity. It can significantly reduce QOL by limiting functional independence and mobility, while also contributing to pain, fatigue, and secondary complications such as contractures and pressure ulcers (143).

1.5.4.2 Pathophysiology

Physiologically, the descending pathways originating in the brainstem and the motor cortex send inhibitory signals to interneurons and motoneurons, thereby enabling the execution of smooth and coordinated movements. In the case of SCIs, this organization is disrupted, functionally isolating the SC from the modulatory influence of higher centers and facilitating the development of neuronal hyperexcitability. Some studies have shown that several mechanisms contribute to the development of spasticity (144), the main ones being as follows:

- **Increased excitability of motoneurons:** it can be explained by the presence of excessive Persistent Inward Currents (PICs) and the loss of control over the Excitatory Post-

Synaptic Potentials (EPSPs) by the descending pathways, making the motoneurons excessively responsive to the afferent inputs (145,146).

- **Increased excitability of interneurons:** following SCI, several excitatory interneurons became hyperexcitable leading to exaggerated responses even in case of harmless stimuli (72).
- **Axonal sprouting:** is involved in the development of spasticity through the aberrant reinforcement of neural circuits and via the maladaptive plasticity (147).

1.5.4.3 Clinical presentation

Spasticity presents with a wide spectrum of motor manifestations that reflect the loss of supraspinal inhibitory control over spinal reflex circuits (142). Clinically, is characterized by a triad consisting of a velocity-dependent increase in resistance to passive movement, elevated muscle tone at rest and clonus, that is a rhythmic pattern of contractions typically elicited by sudden stretch most commonly in the lower limbs. Patients may also exhibit involuntary spasms arising from disinhibited polysynaptic reflexes, such as the flexor withdrawal reflex. These spasms can be triggered by nociceptive, cutaneous or visceral inputs (bladder distension, bowel stimulation, skin irritation or pain). In addition, sustained abnormal posturing of the limbs and trunk represents another common clinical feature (148,149). Overall, these phenomena highlight the complex and multifaceted clinical expression of spasticity, which evolves over time due to ongoing neural plasticity and secondary changes in muscle and connective tissue properties.

1.5.4.4 Evaluation

Before beginning treatment, it is essential to conduct a thorough and accurate assessment in order to determine the spasticity severity.

Clinical scales

The most widely used scale is the Modified Ashworth Scale (MAS), which estimate the resistance during passive movements of limbs. It consists of a scoring system ranging from 0 to 4, with an additional intermediate grade of 1+. The scale is quick to administer and does not require specialized equipment, making it practical for clinical use; however, its reliability is limited by the influence of by non-neural factors, such as muscle stiffness, contractures, the speed and variations in testing speed and joint position. Moreover, the MAS provides little information related to the functional impact of spasticity on motor performance (150,151). Despite these shortcomings, it is still considered a useful “global” indicator of muscle resistance and therefore is essential in the follow-up.

Grade	Description
0	No increase in muscle tone
1	Slight increase in muscle tone, manifested by a catch and release or by minimal resistance at the end of ROM when the part is moved
1+	Slight increase in muscle tone, manifested by a catch, followed by minimal resistance throughout the remainder (less than half) of the ROM
2	More marked increase in muscle tone through most of the ROM, but the affected part(s) is easily moved
3	Considerable increase in muscle tone, passive movement is difficult
4	Affect part is rigid

Table 4: The Modified Ashworth Scale (MAS)

The MAS scale alone is not sufficient and must be supplemented with other scales to provide a comprehensive evaluation of spasticity. The Tardieu scale, for instance, allows a clinically meaningful distinction between neural and mechanical components of hypertonia by comparing the ROM during fast stretch (R1) with the passive ROM obtained during slow stretch (R2) (152). In addition, the Penn Spasm Frequency Scale (PSFS) is a subjective assessment designed to quantify episodic spasms and understand their impact on the patient's daily activities (151,153).

Biomechanical assessment

Although rating scales are the primary tool for assessing spasticity, they have limitations due to the examiner's technique and the mechanical properties of the muscle. For this reason, biomechanical assessment plays a key role by providing objective measurements that help distinguish reflex-mediated resistance (typically observed during high-velocity stretch) from non-neural stiffness (evident at low velocities). Isokinetic dynamometers are widely used in this context, as they apply controlled passive joint movements at predefined speeds to quantify muscle torque, reflecting resistance to stretch. These measurements are often combined with surface EMG analyses to provide reference measurements for standardization. Several studies have reported a strong correlation between dynamometric measures and clinical scales such as the MAS (151,154). However, the use of dynamometers remains limited due to cost and technical demands. Another commonly used method is the pendulum test, originally described by Wartenberg, which involves passively extending the lower limb and allowing it to swing freely under the influence of gravity. The resulting oscillatory movement is then analysed, typically revealing reduced amplitude and diminished duration of oscillations in individuals with spasticity. Even though is a simple and non-invasive test, it is influenced by the patient's ability to relax, it can only be use for the knee joint and is less informative in cases of severe spasticity (151,155).

Electrophysiological assessment

Electrophysiology provides insight into spinal circuits, offering information that cannot be captured through clinical examination. Because spontaneous EMG activity is typically associated with dystonia or muscle spasms, the evaluation of spasticity requires elicitation of reflex responses rather than measurements at rest. The most commonly used tests include the H-reflex, obtained through peripheral nerve stimulation, the T-reflex elicited by tendon percussion, and the stretch reflex induce by passive muscle elongation. These measures assess the behavior of Ia afferent–motoneuron pathways and quantify parameters such as latency, amplitude, recovery cycles, and reflex thresholds. In patients with spasticity, these responses have been found to be more powerful than those of the general population (151,156,157).

1.5.4.5 Treatment

The management of spasticity requires an individualized and multi-layered approach that considers both the underlying neurophysiological mechanisms and the patient's functional needs. In some cases, spasticity may also provide functional benefits, such as improving postural stability during sitting or standing, facilitating transfers and certain activities of daily living, maintaining muscle mass, and promoting venous return, thereby potentially reducing the risk of deep venous thrombosis. This dual role should be carefully considered during the planning of treatment strategies. Spasticity often follows a fluctuating course and may be exacerbated by factors such as urinary tract infections, constipation, bladder distension, cold exposure, or emotional stress. Identifying and addressing these triggers is a crucial step, as their removal may significantly alleviate symptoms without the need for more intensive antispastic interventions (150).

Physical interventions

The aim of physical therapy is to ensure that the viscoelastic properties of muscles, connective tissue, and joints are maintained, while preserving ROM and preventing the development of contractures. Rehabilitation programs include a variety of exercises, such as standing and active movement. However, in cases of severe spasticity, passive mobilization and stretching are preferred (148).

Pharmacological treatments

1. Peroral medications

Oral medications constitute the first-line pharmacological approach for the management of spasticity. Among these, baclofen is the most used; it is a GABA analogue that exerts its action by binding to GABA-B receptors, particularly, on Ia sensory afferent neurons, interneurons, and motoneurons, thereby reducing neuronal excitability. Benzodiazepines, such as clonazepam and

diazepam, instead enhance GABA-A receptor activity and are remarkably effective for nocturnal muscle spasms and stiffness. Additional agents, including thiazidine, clonidine, and gabapentin, have also demonstrated efficacy in reducing spasticity (148,150).

2. Focal pharmacological treatment

When spasticity is limited to a small number of muscles, focal approaches are generally preferred. Botulinum toxin injection represents the most widely used approach; produced by *Clostridium Botulinum*, it inhibits acetylcholine release at the neuromuscular junction. Type A toxin is most employed, and its effects are temporary and reversible. For optimal outcomes, injections should be combined with targeted physical therapy (158). An alternative valid option could be the local administration of phenol, which induces chemical neurolysis and provides a longer lasting, but irreversible, reduction in muscle activity (148,150).

3. Intrathecal therapies

In cases of severe or refractory lower-limb spasticity, intrathecal baclofen therapy is recommended. This involves the surgical implantation of a programmable baclofen-delivery pump in the abdomen, which delivers baclofen directly into the subarachnoid space via an intrathecal catheter. Owing to the high density of GABA receptors in the lumbar segment of SC, the therapeutic efficacy can be achieved with relatively low doses, thereby minimizing systemic side-effects. Treatment administered over long periods of time has been shown to have sustained therapeutic benefits (148,150,159).

Surgical and neuromodulatory strategies

Surgical treatments entail procedures that are irreversible. One example is posterior selective rhizotomy, which is considered for patients with severe and refractory regional spasticity (150). In parallel, neuromodulation techniques, particularly SCS, have gained increasing attention as a promising therapeutic option proving to be a potentially effective tool for controlling post-SCI spasticity. This has been achieved through high-frequency stimulation protocols that have enabled the inhibition of hyperreflexia and co-contraction (160).

1.5.5 Neuropathic Pain (NP)

1.5.5.1 Definition

Neuropathic pain (NP) is a disabling chronic condition and one of the main neurological complications after a SCI, affecting approximately 65-90% of patients. It results from the damage to the somatosensory system, including both peripheral fibers and central neurons. Although, its

onset may occur at any stage after the injury, it usually develops during the chronic phase, reflecting the maladaptive plasticity changes in the nervous system. Furthermore, NP represents a heterogeneous entity driven by multiple pathophysiological mechanisms, which contribute to its clinical complexity and therapeutic resistance. Its presence is associated with a significant reduction in QOF contributing to sleep disturbances, mood disorders, and decreased functional independence. It is also important to distinguish NP from nociceptive pain, in its visceral and musculoskeletal components, which may coexist after the trauma but require different therapeutic approaches (124,161).

1.5.5.2 Pathophysiology

The development of NP is characterized by a series of complex and dynamic mechanisms that cause alterations at both central and peripheral nervous systems. Initially, it was thought to depend primarily on structural and functional alterations at the site of injury; however, increasing evidence indicate that widespread changes along the neuroaxis contribute to the onset of this condition (162,163). Below-level pain has been associated with degeneration of spinothalamic pathways and GABA-mediated inhibition (164). At the spinal level, injury-induced deafferentation triggers extensive reorganization of dorsal horn circuits, characterized by increased excitatory glutamatergic transmission, NMDA receptor activation, and loss of inhibitory intraneuronal control, collectively driving central sensitization and amplification of sensory inputs (165,166). These processes are further sustained by neuroinflammatory processes, changes in ion channel expression, neurotrophic factors, and receptor systems (dopaminergic and cannabinoid pathways) (167–169). Beyond the SC, also supraspinal regions such as the thalamus, somatosensory cortex, prefrontal cortex, and limbic system undergo significant structural and functional reorganization contributing to altered sensory integration and persistent pain perception. Notably, the size of this central reorganization has been shown to correlate with both pain intensity and duration, remarking the critical role of long-term neuroplasticity in the maintenance of NP (170,171).

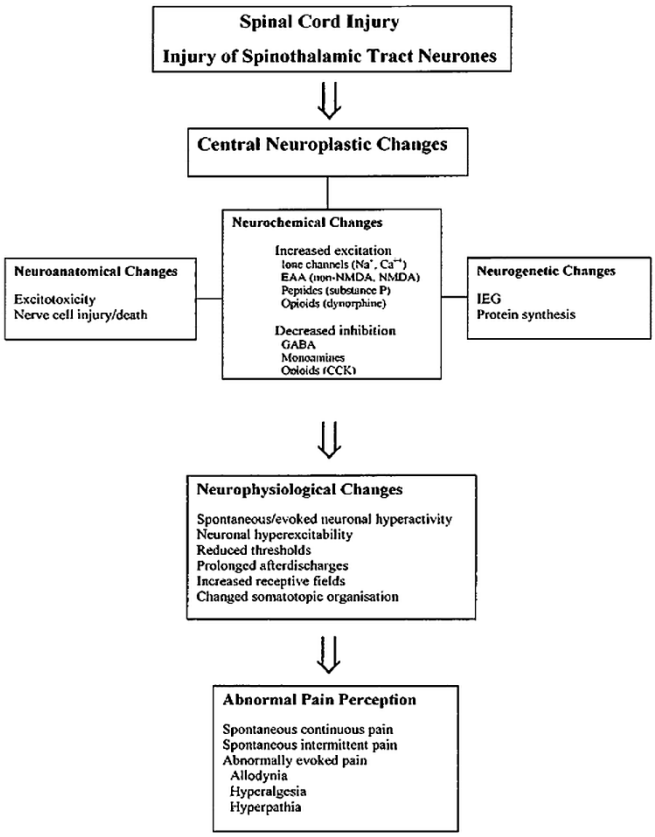


Figure 19: Pathophysiology of Neuropathic Pain
Source: Eide, P. K. (1998). Pathophysiological mechanisms of central neuropathic pain after spinal cord injury. Spinal Cord, 36(9), 601–612.

1.5.5.3 Clinical presentation

The International Association for the Study of Pain (IASP) classified the NP based on the level of the injury by breaking it down into:

- **At-level NP:** it occurs within a few dermatomes surrounding the neurological level of injury and typically presents with an earlier onset;
- **Below-level NP:** it is usually more diffuse, associated with central mechanisms, and tends to develop later.

Clinically, NP is commonly described as burning, shooting, stabbing, or electric shock-like. It may manifest as spontaneous pain, either continuous or intermittent, or as stimulus-evoked pain; the latter type encompasses allodynia and hyperalgesia. Patients frequently experience other associated sensory abnormalities, including paraesthesia and dysesthesia. The clinical course of NP is generally chronic and variable over time, with symptom fluctuations influenced by factors such as stress, fatigue, and environmental conditions. Importantly, NP is often poorly responsive to conventional analgesic therapies, representing a significant therapeutic challenge (172,173).

1.5.5.4 Evaluation

The assessment of NP is complex and requires a multidisciplinary approach that combines clinical examination with validated tools. However, before conducting this assessment, it is important to determine the NLI and the characteristics of the pain (location, distribution, intensity, quality, and duration) through a patient interview. Pain evaluation is performed using validated scales and neurophysiological techniques (161).

Neuropathic pain evaluation scales

Various validated instruments are available for the assessment of NP, enabling a multidimensional clinical features evaluation. Among these, it is important to mention the Douleur Neuropathique 4 (DN4) (174), which is widely used as a screening tool to support the diagnosis of NP and the Neuropathic Pain Symptoms Inventory (NPSI) (175), which provides a detailed characterization of pain quality, allowing the evaluation of symptom profiles and their evolution over time, as well as the response to treatment. These tools are commonly complemented by unidimensional scales such as the Numerical Rating Scale (NRS) or the Visual Analog Scale (VAS), that are used to quantify pain intensity (161).

Neurophysiological techniques

Electrophysiological assessment of NP generally relies on QST and laser-evoked potentials (LEPs). QST evaluates sensory and pain thresholds through standardized thermal and mechanical stimuli, allowing the detection of both loss and gain of function (such as allodynia and hyperalgesia) across different afferent fibre types (Aβ, Aδ, and C) and providing a comprehensive view of the somatosensory system functionality (116). In contrast, LEPs represent a more objective and pathway-specific method, by selectively activating nociceptive fibers (Aδ and C) through laser stimulation of the skin and recording the resulting cortical responses. In individuals with NP, these responses are typically altered, showing changes in both latency and amplitude, reflecting dysfunction of nociceptive pathways (161).

1.5.5.5 Treatment

The management of NP is primarily focused on symptoms control and include a wide range of therapeutic strategies, from pharmacological interventions to more invasive approaches such as surgical procedures and neuromodulation techniques (161,173,176).

Pharmacological treatments

In the past, pain following SCIs was treated with anti-inflammatory drugs; however, evidence has proved that these are more effective in treating nociceptive pain than NP, for which other classes

of medications are required. The first-line treatment NP involves the use of antidepressants and antiepileptic medications. Among antidepressants, tricyclic antidepressants (such as amitriptyline) and serotonin-noradrenaline reuptake inhibitors (such as duloxetine) have been shown to be effective in reducing NP, likely due to their action on descending modulatory pathways (177). Among antiepileptic drugs, mostly gabapentin and pregabalin have shown better results due to their ability to reduce central pain sensitization, which is attributed to their action on voltage-gated calcium channels (178). Second-line medications, on the other hand, include lidocaine, which blocks sodium channels, and tramadol, which has a dual action by interacting with opioid receptors and inhibiting the serotonin-noradrenaline reuptake.

Stimulation techniques

Neuromodulation techniques have emerged as valuable therapeutic options in the management of NP, particularly in patients with refractory symptoms. This strategy aims to modulate abnormal neural activity within pain pathways through targeted stimulation of peripheral nerves, SC, or supraspinal structures.

1. Transcutaneous Electrical Nerve Stimulation (TENS)

Transcutaneous Electrical Nerve Stimulation (TENS) is a non-invasive neuromodulation technique used to reduce pain through the electrical stimulation of peripheral nerves. Its analgesic effects are primarily mediated by activation of the gate-control mechanism and enhancement of endogenous inhibitory pathways. TENS achieves better results at the site of the injury and in patients with incomplete SCI (179).

2. Spinal Cord Stimulation (SCS)

SCS represents a promising option for patients who do not respond to conventional pharmacological therapy. Its functioning is based on the gate control theory delivering electrical pulse through leads placed in the epidural space. Traditional monophasic stimulation alleviates pain by replacing it with paresthesia in the affected area. Research into this field has led to the development of burst and high-frequency stimulation patterns that have been shown to provide a better pain relief and a paraesthesia free-stimulation (180,181). The success of SCS depends strictly on patient selection based on various parameters, such as sensory phenotype and the degree of central sensitization.

3. Deep Brain Stimulation (DBS)

The DBS involves the direct stimulation of the thalamus, periventricular gray matter, internal capsule, and motor cortex. It is a fairly invasive procedure that is selected when all previously discussed strategies have failed to treat NP (182).

Surgical ablative treatments

For the management of NP below the site of the lesion, several neurosurgical ablative procedures, such as cordectomy and Dorsal Root Entry Zone (DREZ) lesions, have been proposed aiming to irreversibly interrupt pain transmission pathways in a more or less selective manner. However, their use remains controversial and is currently limited, as their clinical efficacy is not well established and they are associated with a significant risk of neurological complications (161,176).

1.6 Strategies for spinal cord repair

Following SCI, the lesion is organized into three distinct tissue compartments, each characterized by specific structural and biological features that influence the potential for recovery. From the center outward, these encompass the lesion core, the surrounding astrocytic scar, and the adjacent residual neuronal tissue, as previously described in Chapter 1.4. Although functional recovery after SCI was traditionally thought to require restoration of the original anatomical organization, accumulating evidence has challenged this concept. It is now recognized that precise point-to-point reconnection is not necessary; rather, recovery can be achieved through various adaptive mechanisms of neural plasticity, including axonal sprouting, synaptic reorganization, and the creation of alternative relay pathways. These compensatory circuits enable cortical signals to reach spinal motor networks indirectly, effectively bypassing disrupted supraspinal connections. Furthermore, it has been demonstrated that the SC acts as a smart information-processing interface; in fact, even in the absence of supraspinal control, central generator patterns (CGPs) located below the lesion level are capable of using afferent inputs to produce muscle activation, enabling complex motor behaviours such as standing and walking. This evidence therefore suggests that sensory information coming from the regions below the injury alone may be sufficient to significantly improve motor control following SCI (183,184). To effectively develop repair strategies, it is essential to understand how post-SCI neural reorganization differs between complete and incomplete lesions.

Incomplete SCI: modulating circuit reorganization

In incomplete SCIs, functional recovery relies predominantly on the capacity of spared neural circuits to undergo adaptive reorganization rather than on axonal regeneration. Experimental studies in animal models have extensively demonstrated these plastic changes (185,186), while indirect evidence suggests that similar mechanisms also occur in humans (187,188). After the injury, a portion of descending pathways (including corticospinal, reticulospinal, rubrospinal, and serotonergic fibers) remain anatomically preserved. These residual projections undergo collateral sprouting and establish new synaptic connections with spinal neurons located above and below the lesion. Notably, propriospinal interneurons can form detour circuits that bypass the injured segment, thereby enabling supraspinal signals to reach distal motor networks through alternative pathways. Sensory afferent input, especially proprioceptive feedback, plays a crucial role in driving and refining this reorganization, as spinal circuits below the lesion continue to process peripheral sensory information. It has been shown that disruption of proprioceptive inputs markedly impairs the remodelling of descending pathways compromising the functional recovery. However, maladaptive plasticity may also occur as aberrant sprouting of sensory afferents can

contribute to spasticity, neuropathic pain, and altered motor function. These adaptive changes are supported by molecular mechanisms that regulate synaptic efficacy, including modulation of glutamatergic transmission, remodelling of inhibitory GABAergic and glycinergic signaling, and alterations in presynaptic neurotransmitter release. Glial cells also actively contribute through synaptic pruning, secretion of synaptogenic factors, and modification of extracellular matrix components. Conversely, extracellular matrix molecules, such as chondroitin sulphate proteoglycans (CSPGs), and Nogo-associated proteins, restrict plasticity and stabilize existing networks. Consequently, the emerging therapeutic strategies focus not only on promoting axonal regeneration, but also on enhancing adaptive synaptic plasticity and facilitating the functional reorganization of residual spinal circuits (184).

Complete SCI: restoring connectivity

In complete SCIs, communication between supraspinal centers and spinal neurons is interrupted due to the loss of axonal continuity. In the adult CNS, the intrinsic regenerative capacity of neurons is limited, and the post-injury microenvironment further restricts axonal regrowth. In particular, the non-neural lesion core is characterized by inhibitory extracellular matrix components, including chondroitin-sulphate proteoglycans and myelin-associated inhibitors, which make it a non-permissive environment for neural regeneration (189). Moreover, successful recovery depends not only on axonal regrowth but also on the restoration of functional synaptic connectivity. Experimental studies have shown that axonal elongation in the absence of appropriate synaptic integration does not result in meaningful functional improvement. Consequently, current regenerative strategies aim not only to promote axonal regeneration but also to recreate favourable conditions for the reconstruction of functional neural circuits. A first approach consists of enhancing the intrinsic growth capacity of adult neurons through modulation of molecular pathways associated with neuronal plasticity and regeneration, including phosphatase and tensin homolog (PTEN), mechanistic target of rapamycin (mTOR), signal transducer and activator of transcription 3 (STAT3) and suppressor of cytokine signaling 3 (SOCS3). Axonal growth may be powerfully supported by inflammatory mediators and growth-promoting molecules, such as Toll-Like Receptor 2 (TLR2) agonists, oncomodulin, zymosan, brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), and laminin, which can also help guide regenerating axons toward appropriate targets (22). Despite promising results obtained in animal models, functional recovery in humans remains limited, highlighting that anatomical regeneration alone is insufficient without adequate functional integration of newly established neural connections (184).

Feature	Incomplete SCI	Complete SCI
Tissue architecture	Partial preservation of white matter tracts and interneuronal networks	Complete disruption of axonal continuity, with the lesion core separating supraspinal and sub-lesional spinal segments
Biological substrate for recovery	Residual descending pathways, propriospinal interneurons and sensory afferents below the lesion	Intrinsically functional spinal circuits below the lesion, which are isolated from supraspinal control
Capacity for circuit reorganization	High and guided, supported by residual descending pathways and shaped by sensory feedback	High and unguided because of the absence of supraspinal modulation
Risk of maladaptive plasticity	Moderate	High
Mechanisms responsible for maladaptive plasticity	Partial inhibition loss and altered excitation-inhibition balance	Uncontrolled sprouting, altered excitation-inhibition imbalance and hyperexcitability of spinal circuits
Primary mechanisms enabling functional recovery	Adaptive reorganization of spared pathways, recruitment of detour circuits and sensory-driven refinement of spinal networks	Restoration of connectivity across the lesion is required

Table 5: Biological feature differences between Complete and Incomplete SCIs

1.6.1 Biological strategies for repair

1.6.1.1 Strategies for secondary damage reduction

Modern biological strategies for spinal cord repair mainly aim to limit secondary damage and create a microenvironment favourable to neural regeneration (184,190). A first approach consists in reducing inflammation through biomaterials used as carriers for anti-inflammatory drugs, such as Baricitinib (JAK1/2 inhibitor), or through the administration of nitric oxide (NO), capable of modulating the immune response (191,192). Concurrently, several strategies target oxidative stress caused by ROS. Among these, polyethylene glycol (PEG) has shown neuroprotective effects, while biodegradable manganese-doped and resveratrol-functionalized silica nanoparticles (PMMSN-RES) allow for more specific and effective antioxidant action (193,194). Another key goal is the restoration of the blood-medullary barrier (BSCB), which is frequently compromised

after SCI. In this context, curcumin-loaded polyacetals have been associated with a reduction in inflammation and an increase expression of tight junctions, promoting barrier stabilization (195). Additionally, carrier biomaterials are used to transport mesenchymal stem cells to the lesion site, improving their survival and therapeutic efficacy (196). Finally, particular focus is on the reduction of the glial scar, one of the main obstacles to axonal regeneration. Composite hydrogels based on alginate, chitosan and genipin have been developed to decrease astrocytic reactivity through extracellular calcium sequestration, thus limiting secondary calcium-mediated damage. Similarly, chondroitinase ABC (ChABC) encapsulated within self-assembling peptide hydrogels promotes glial scar degradation, facilitating axonal regrowth and functional recovery (197,198).

1.6.1.2 Increasing neural regeneration

Bio-scaffolds

Scaffolds are 3D porous structures that act as structural support and can drive axonal growth. In addition to their mechanical function, they are engineered to mimic the biochemical and physical properties of the extracellular matrix (ECM), often incorporating neurotrophic factors, bioactive molecules, or cellular components in order to create a microenvironment suitable for tissue repair. For this reason, scaffold-based approaches represent a new frontier in the treatment of SCIs. According to their composition, scaffolds can be broadly classified into:

- **Natural scaffolds:** composed by biocompatible materials such as collagen, fibrin, chitosan, agarose, and alginate, which closely resemble the native ECM and promote cell adhesion;
- **Synthetic scaffolds:** commonly fabricated from biodegradable polymers or conductive hydrogels, which offer greater control over mechanical properties, degradation rate, and electrical conductivity;
- **Mixed scaffolds:** they combine natural and synthetic materials to optimize both biocompatibility and structural performance. Among these, chitosan-based scaffolds composite with graphene oxide (GO) have attracted considerable interest because of their enhanced mechanical strength, electrical conductivity, and potential to support neuronal regeneration (190,199–205).

A recent promising regenerative strategy for post-SCI damage repair involves the use of bioactive scaffolds merged with molecular therapies. McGuire et al. developed a collagen-based scaffold functionalized with PTEN-siRNA designed to suppress the expression of PTEN, which is a potent inhibitor of axonal regeneration. The results showed a reduction in PTEN expression and increased axonal growth at the scaffold implantation site (206). Overall, these approaches

highlight the potential benefits of combining tissue engineering strategies and gene modulation to drive neural regeneration after SCI.

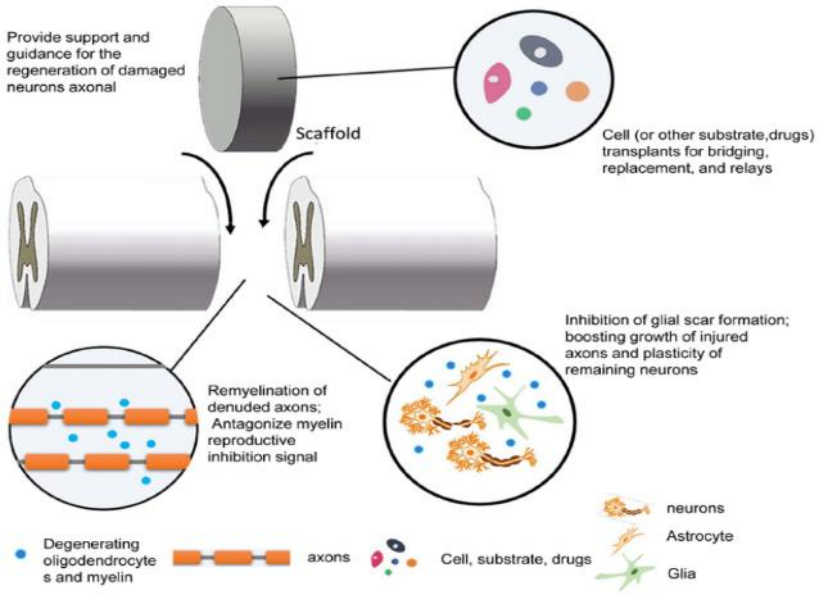


Figure 20: Scaffold-based Spinal Cord repair strategy.
Source: Liu, S., Xie, Y. Y., & Wang, B. (2019). Role and prospects of regenerative biomaterials in the repair of spinal cord injury. Neural regeneration research, 14(8), 1352–1363.

Cellular transplantation

Cell transplantation is currently one of the most extensively investigated strategies and it is addressed to cases in which tissue loss is very extensive and cannot be reconstituted by endogenous repair processes. In addition to replacing lost cellular components, transplanted cells can modulate the lesion microenvironment at the lesion site by promoting neuroprotection, reducing inflammation, and supporting regenerative processes. Several cell populations have been explored for this purpose, including Schwann cells, oligodendrocyte precursor cells, and mesenchymal stem cells (207). Preclinical studies conducted in both rodent and primate models have demonstrated that these grafts can enhance axonal regeneration and remyelination, thereby restoring communication between the areas separated by the injury. Despite these promising findings, cell transplantation alone is generally insufficient to achieve complete functional recovery. Therefore, current evidence supports the integration of cell-based therapies with complementary therapeutic approaches in order to maximise regenerative outcomes (92).

1.6.2 Engineering strategies for spinal cord repair

Modern therapeutic strategies for SCIs are transforming the field of neurorehabilitation through the integration of neurosurgery, neuroengineering, robotics, and computational neuroscience. In recent years, numerous wearables and implantable neurotechnologies, such as neuroprosthesis, exoskeletons, and electrical stimulation systems, have been developed with the aim of recovering or enhancing impaired motor functions. The common principle of these technologies is to harness the capacity and plastic potential of spared neural circuits by promoting neuronal reorganization through training and targeted stimulation. Emerging clinical evidence suggests that such neurotechnologies can substantially improve functional outcomes and open up very promising prospects for the future treatment of SCIs. Engineering-based interventions may act through multiple mechanism, including the modulation of spinal circuits, the restoration of the supraspinal pathways control through bypass systems and the guidance of plasticity in an adaptative way (184).

1.6.2.1 Activation and modulation of spinal execution circuits

Following SCI, sensorimotor circuits located below the lesion often remain anatomically preserved but functionally disconnected from the supraspinal control. Nevertheless, evidence suggests that some descending pathways, particularly reticulospinal tracts, may remain partially spared even in severe cases. Neuromodulation strategies, especially epidural or transcutaneous spinal cord stimulation, aim to reactivate these residual networks by directly targeting spinal sensorimotor circuits. The electrode paddle is applied dorsally to the SC in order to activate the large proprioceptive fibers, thereby increasing the excitability of premotor interneurons and motoneurons embedded in the corresponding spinal segments. This enhanced excitability facilitates the integration of residual descending inputs with sensory feedback, ultimately enabling the generation of functional motor output (208–210). Spatiotemporal stimulation has given better results than continuous stimulation. Unlike continuous stimulation, spatially selective closed-loop protocols deliver short bursts of electrical stimulation synchronized with the physiological timing of motor activity, resulting in more coordinated and natural movements (211,212). These approaches have demonstrated refined control of paralyzed lower limbs in both animal models and humans while also promoting activity-dependent plasticity within spinal neural circuits (213). This mechanism appears particularly relevant in incomplete SCI, where spared supraspinal pathways can be amplified and integrated into reorganized propriospinal relay networks, supporting functional recovery. In complete SCI, neuromodulation can still activate spinal

locomotor and sensorimotor circuits below the lesion, while restoration of voluntary motor control remains limited in the absence of residual top–down input.

1.6.2.2 Engineering strategies to bypass the lesion

Brain–Computer Interfaces (BCIs) represent one of the most advanced and innovative strategies for functional recovery after SCI because they enable the creation of an artificial link between the brain and the nervous or muscular structures located below the lesion level. Their function relies on the recording of the cortical signals associated with motor intentions, followed by signal decoding and wireless real-time transmission to an epidural electrode array positioned over the SC, thereby bypassing the disruption of descending pathways caused by the SCI. Several studies have shown the motor improvements obtained through brain-spine interfaces; particularly for restoring movements of the upper limbs but also BCIs can be used to re-establish sensory feedback by converting tactile information from robotic prosthesis into direct stimulation of the somatosensory cortex (213–216). Despite promising results, large-scale clinical application remains limited by significant technological and practical challenges, including the need for invasive brain implants, the low stability of neural signals over the time, the high computational complexity of decoding system, and the substantial economic costs associated with device implementation and long-term management.

1.6.2.3 Engineering rehabilitation to increase adaptive plasticity

Rehabilitation primarily relies on activity-based therapies, which focuses on repetitive movements and sensorimotor activation to enhance adaptive neuroplasticity. To further potentiate these mechanisms, several neuromodulation approaches have been developed, including electrical stimulation of the motor cortex and SC, as well as transcranial magnetic stimulation (217,218). Experimental studies have demonstrated that combining intensive rehabilitation with robotic assistance and neuromodulatory interventions can facilitate the recovery of voluntary motor function even in patients with severe paralysis (219). Functional recovery is thought to result from the reorganization of spared neural pathways, whereby the brain establishes alternative connections to transmit motor commands below the level of injury. Despite these promising advances, current technologies remain limited by high costs, technical complexity, and reduced practicality in daily life, which is why many patients continue to prefer the wheelchair. Nevertheless, ongoing developments in implantable devices and home-based neurorehabilitation systems may improve the accessibility, usability, and long-term effectiveness of these therapeutic strategies.

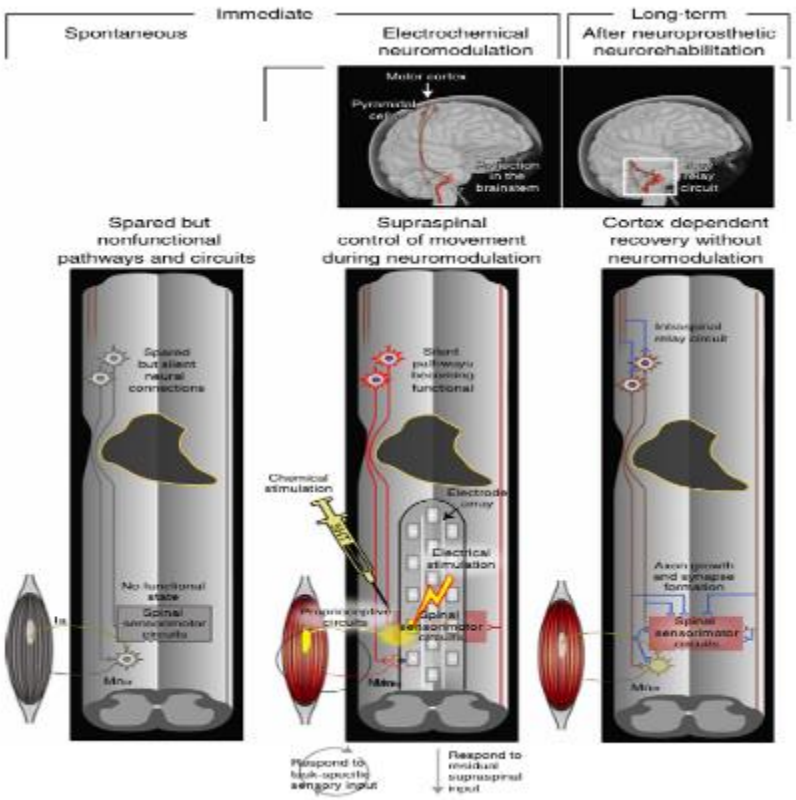


Figure 21: Engineering strategies used for Spinal Cord Repair.
Source: Courtine, G., & Sofroniew, M. V. (2019). Spinal cord repair: advances in biology and technology. Nature medicine, 25(6), 898–908.

Strategy	Category	Technique
Neuromodulation	Activation and modulation of SC execution circuits	Transcutaneous Electrical Stimulation (TES)
		Spinal Cord Stimulation (SCS)
		Intraspinal Microsimulation (ISMS)
		Pharmacological modulation (monoaminergic agents)
Neuroprosthetics	Restoration of descending pathways through neuroprosthetic bypass	Brain-Computer Interfaces (BCI)
		Brain-Spine Interfaces (BSI)

Table 6: Summary table of various Spinal Cord Repair engineering techniques

1.7 Spinal Cord Stimulation (SCS)

1.7.1 Spinal cord stimulation device and surgical procedure

The Spinal Cord Stimulation (SCS) is a now validated tool for the treatment of NP refractory to pharmacological therapies. Recently, SCS has also emerged as a promising strategy for motor recovery in subjects with various neurological disorders, such as stroke or SCIs. The SCS system consist of three main components (220–222):

- **Electrodes or leads**, which may be cylindrical (inserted through an epidural needle) or paddle-shaped (surgically implanted via laminotomy) and they are typically made of platinum or platinum-iridium alloys. The leads connecting the electrodes to the pulse generator are coated with medical-grade silicone or polyurethane in order to provide both flexibility and mechanical durability while ensuring adequate electrical insulation and preventing current leakage.
- **Implantable pulse generator (IPG)**, that is the rechargeable internal battery-powered unit responsible for generating and delivering electrical pulses to the leads. The IPG casing is manufactured with titanium, whose biocompatible and inert properties minimize the risk of adverse tissue reactions; while also giving resistance to the mechanical stresses associated with body movements and device implantation.
- **External charging and reprogramming equipment**, which include the charger and the remote controller for setting the stimulation parameters.

The SCS system implantation requires careful preoperative planning and accurate electrode placement. In NP management, electrodes are typically positioned at the T6–T8 level. Conversely, in SCI protocols, placement is usually targeted at conus medullaris (particularly T10–L1 or T10–T12) to recruit spinal roots innervating the lower limbs and achieve functional outcomes. In order to assure optimal precision, preoperative MRI data combined with intraoperative fluoroscopic imaging can be employed to guide the procedure and confirm the correct positioning. In the management of NP, the surgery typically involves a two-stage approach including a trial period followed by permanent device implantation. During the first phase, percutaneous electrodes are introduced into the epidural space and secured externally using sutures or skin glue. The externalized ends of the leads are then connected to an external temporary pulse generator for evaluating the clinical efficacy. Patients who demonstrate a favourable response proceed to definitive implantation, in which the leads are fully internalized and tunnelled subcutaneously to a permanent implantable pulse generator, typically in a subcutaneous pocket located in the gluteal region (223). Instead, when the SCS is aimed at post-SCI motor recovery, neurosurgeons perform

the permanent paddle implantation technique through a partial laminectomy. Once the electrodes array ais placed an intraoperative electromyographic check is carried out to optimize the position of the paddle. After this process, the leads are tunnelled subcutaneously and connected to IPG located in the lower abdominal wall (224).

Figure 22: The main components of SCS system.
Source: https://news.bostonscientific.com/

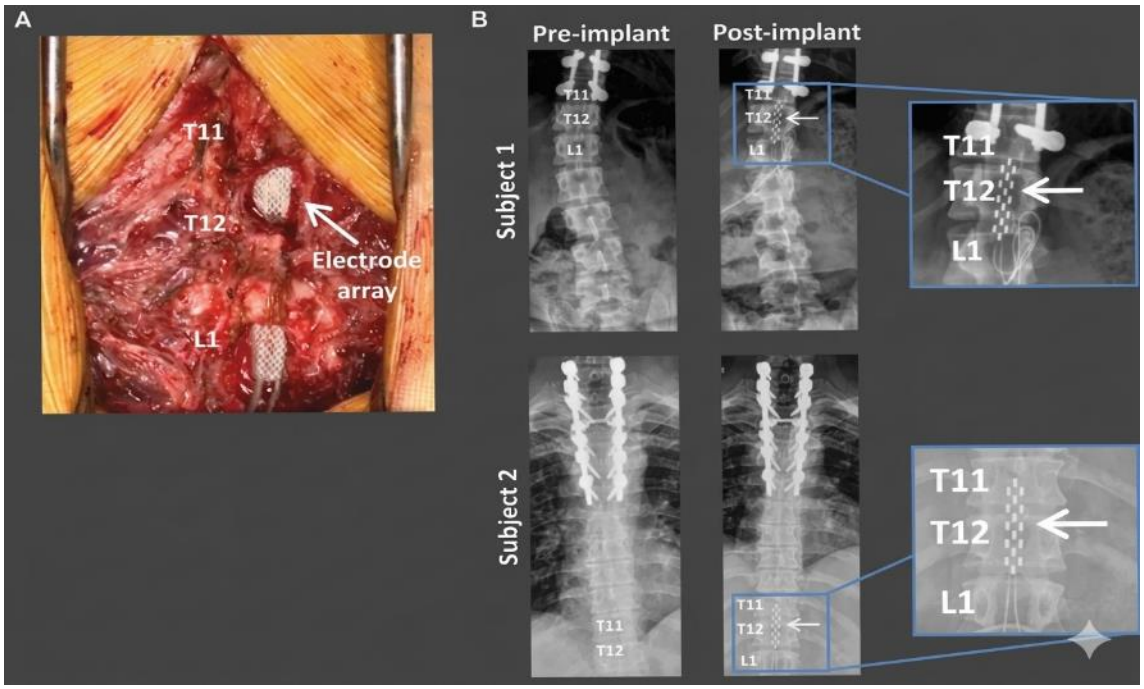


Figure 13: SCS surgical implantation. ***A)*** *Intraoperative image of the electrodes array at T11-L1 levels.* ***B)*** *Anterior-posterior X-ray of two individuals before and after SCS implantation.*
Source: Calvert, J. S., Grahn, P. J., Strommen, J. A., Lavrov, I. A., Beck, L. A., Gill, M. L., Linde, M. B., Brown, D. A., Van Straaten, M. G., Veith, D. D., Lopez, C., Sayenko, D. G., Gerasimenko, Y. P., Edgerton, V. R., Zhao, K. D., & Lee, K. H. (2019). Electrophysiological Guidance of Epidural Electrode Array Implantation over the Human Lumbosacral Spinal Cord to Enable Motor Function after Chronic Paralysis. Journal of neurotrauma, 36(9), 1451–1460.

1.7.2 Spinal cord stimulation: from neuropathic pain treatment to motor function recovery

The SCS has been primarily employed in the management of chronic NP refractory to pharmacological therapy. A large series of evidence has demonstrated the effectiveness of SCS treatment in reducing NP, leading to improvements in quality of life and a decreased reliance on analgesic medications (225). SCS was initially believed to alleviate pain primarily through the gate control theory proposed by Ronald Melzack and Patrick Wall. According to this model, inhibitory interneurons in the *substantia gelatinosa*, integrate afferent inputs from both large-diameter Aβ fibers (touch and proprioception) and small-diameter Aδ and C fibers (pain). Based on prevailing signal, the functional state of the gate can change regulating the transmission of sensory information to higher CNS structures: activation of Aβ fibers inhibits the transmission of nociceptive signals "closing the gate" and alleviating pain, while the activation of Aδ and C fibers "opens the gate" boosting the nociceptive transmission. The NP results from an imbalance of these signals with consequent enhanced transmission through ascending pathways and the amplification of pain perception (226).

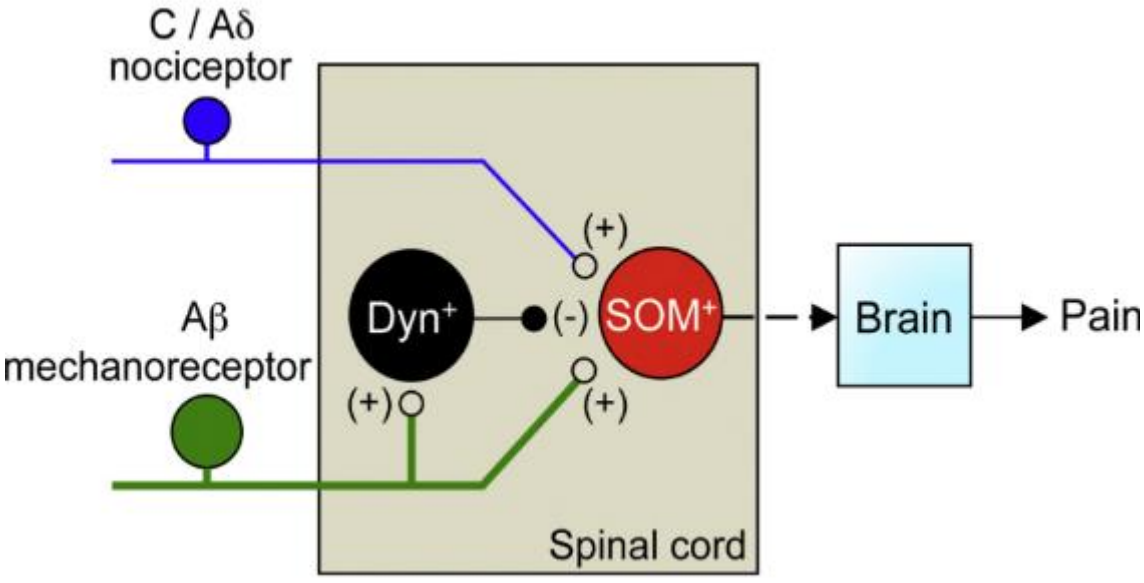


Figure 24: The gate control theory. ***1)*** *SOM: excitatory neurons expressing somatostatin enhancing pain transmission* ***2)*** *Dyn: inhibitory neurons which release dynorphin reducing pain transmission.*
Source: Duan, B., Cheng, L., Bourane, S., Britz, O., Padilla, C., Garcia-Campmany, L., Krashes, M., Knowlton, W., Velasquez, T., Ren, X., Ross, S., Lowell, B. B., Wang, Y., Goulding, M., & Ma, Q. (2014). Identification of spinal circuits transmitting and gating mechanical pain. Cell, 159(6), 1417–1432.

Subsequent research has identified additional mechanisms involved in pain modulation that encompass both spinal and supraspinal processes. Particularly, the Descending Antinociceptive System (DAS) play a key role in pain modulation. The DAS consists of the Periaqueductal Gray (PAG), the Rostral-Ventromedial Medulla (RVM) and the Locus Coeruleus (LC) which release serotonin and norepinephrine at the dorsal horn of the SC promoting spinal inhibition both directly and indirectly via GABAergic interneurons (227). Furthermore, following the injury, reactive gliosis is also observed, and it is characterized by the activation of glial cells and the production of pro-inflammatory cytokines. This neuroinflammatory response makes this system hyperactive and disrupts inhibitory control, thereby contributing to the development and maintenance of pathological nociception (228). Therefore, the mechanism of action of SCS cannot be adequately explained by a simple gate control model. Instead, it reflects a multifaceted modulation of neural circuit interactions across multiple levels of the spinal cord and supraspinal networks, driven by plastic changes that occur after the SCI (225,229). Currently, three principal SCS paradigms are employed for the management of NP:

- **Paraesthesia-based Spinal Cord Stimulation (P-SCS):** it represents the traditional form of neuromodulation for NP, and it sends electrical currents with low frequencies (40-60 Hz) by replacing the painful sensation with a non-painful paraesthesia in the target dermatome. Its analgesic effect is primarily attributed to the activation of large-diameter myelinated Aβ fibers, which suppress nociceptive transmission through spinal inhibitory mechanisms consistent with the gate control theory (230).
- **High Frequency Spinal Cord Stimulation (HF-SCS):** it delivers kilohertz-frequency stimulation leading to paraesthesia-free pain relief. Current evidence suggests that it acts mainly by modulating dorsal horn circuits and local neuroinflammation, but its precise mechanism of action still remains largely unknown (231,232).
- **Burst Spinal Cord Stimulation (B-SCS):** has emerged as an alternative paradigm that delivers packets of high-frequency pulses designed to mimic physiological neuronal burst firing patterns. This approach appears to reduce dorsal horn neuronal excitability through mechanisms that are independent of GABAergic signalling. Furthermore, B-SCS may influence brain networks involved in the cognitive, attentional, and emotional aspects of pain, modulating not only the intensity of the painful stimulus but also its emotional and perceptual processing (233,234).

The application of SCS has progressively expanded from the management of NP to the restoration of motor function, driven by early observations demonstrating that SCS influences not only sensory pathways but also the neural circuits involved in motor control. Specifically, in 1976

Cook reported unexpected improvements in motor function during NP treatment in a patient affected by multiple sclerosis. During the stimulation, this subject regained voluntary control over the upper and lower limbs and demonstrated improved sphincter function (235). Subsequently, Dimitrijevic and colleagues proved that the application of electrical stimulation train at frequencies between 25 and 60 Hz can evoke alternating rhythmic movements of the lower limbs in six paraplegic patients, corresponding to the stance and swing phases of gait. These findings provide evidence for the existence the central pattern generators (CPGs) in humans and support the concept that locomotor-like activity can be produced even without the supraspinal control (236). In the same years, Herman was the first to demonstrate that epidural devices commonly used in the treatment of NP resulted in improved motor function in individuals with incomplete SCI allowing more efficient walking performance with an increased endurance and gait speed associated with a reduction in metabolic demand (237).

1.7.3 Spinal cord stimulation for motor recovery

The SCS has thus emerged as one of the most promising approaches for restoring motor function after a SCI. It involves the delivery of electrical fields through electrode arrays implanted in the epidural space along the dorsal surface of the SC. By targeting the posterior roots and the proprioceptive afferent fibers, SCS increase the excitability of spinal sensorimotor networks below the level of the lesion and promote the integration of the residual descending signals that would otherwise be insufficient to generate movement. Each paddle contact can be programmed independently, allowing highly customizable stimulation strategies, supporting monopolar, bipolar or multipolar configurations depending on the therapeutic requirements. Preserving proprioceptive afferent signalling is essential for effective motor recovery; however, this condition is not fulfilled in humans during continuous stimulation since it induces the deafferentation phenomenon (211). For this reason, the development of stimulation protocols tailored for human application, distinct from those used in murine models, has become necessary. Low-Frequency Spinal Cord Stimulation (LF-SCS), delivered at 20-60 Hz, lead to rhythmic activation of large diameter proprioceptive afferents, generating excitatory postsynaptic potentials in interneurons and motoneurons and contributing in this way to the modulation and facilitation of motor output. LF-SCS is generally applied continuously during the motor task or modulated in a task-dependent manner following a spatiotemporal activation (for instance the phase-specific stimulation during the gait). The stimulation intensity is carefully tuned, usually between sensory and motor thresholds, to increase responsiveness without inducing a conduction block. Another method consists in the use of High-Frequency Spinal Cord Stimulation (HF-SCS). The use of low-amplitude bursts ensures for the same motor neuron activation as continuous stimulation, but

with a lower impact on proprioception erasing, thus representing a more physiological and efficient strategy (211). In addition, HF-SCS has recently been related to a decrease in spasticity resulting in a better quality of life in affected patients (160).

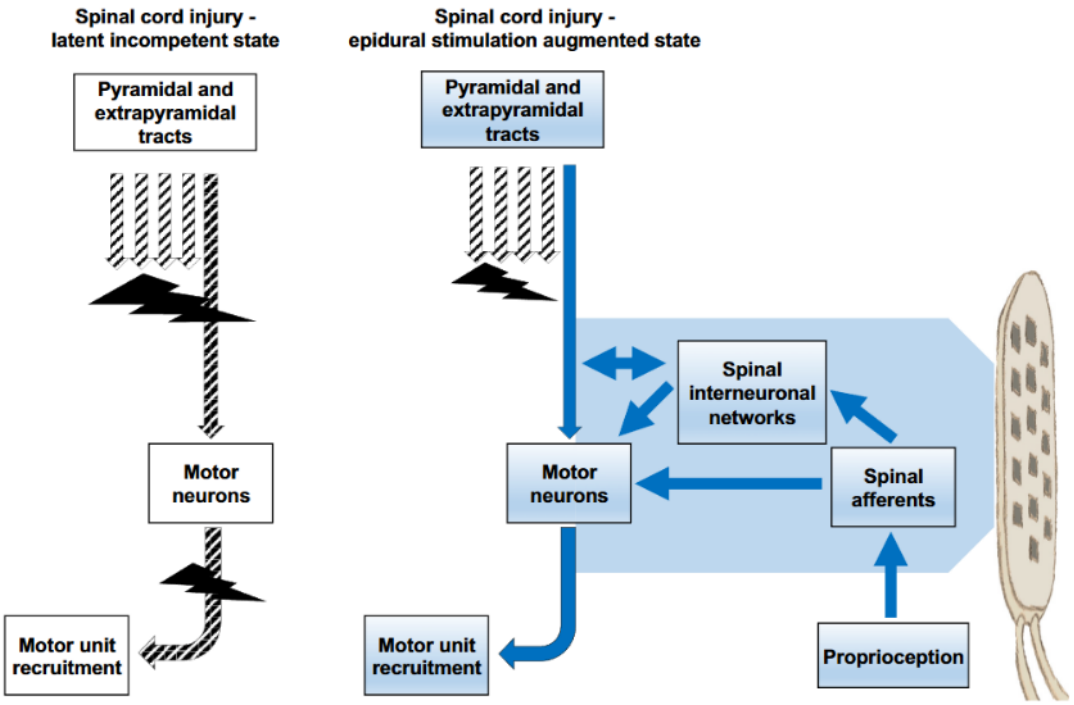


Figure 25: Spinal Cord Stimulation for Motor Recovery.
Together with synergistic proprioceptive inputs, SCS may facilitate task-specific voluntary motor control and support the restoration of complex motor functions, including weight-bearing standing as well as treadmill and overground ambulation.
Source: Hachmann, J. T., Yousak, A., Wallner, J. J., Gad, P. N., Edgerton, V. R., & Gorgey, A. S. (2021). Spinal Cord Stimulation as an intervention for motor recovery after motor complete spinal cord injury. Journal of neurophysiology, 126(6), 1843–1859.

Numerous studies have demonstrated the potential of SCS to promote motor recovery in paraplegic individuals. In 2011, Harkema provided the first clinical evidence that SCS could restore functional lower-limb motor activity in patients with complete SCI. In a participant with chronic high-thoracic AIS-B injury, implantation of a 16-electrodes epidural paddle combined with intensive rehabilitation enabled weight-bearing standing for several minutes and the generation of locomotor-like stepping patterns when stimulation was paired with targeted proprioceptive input. After seven months of combined training and stimulation, voluntary control of the lower extremities re-emerged (238). These initial findings were subsequently supported by Angeli and colleagues, who reported restoration of voluntary motor function within one month of

SCS initiation in three additional individuals with AIS-A and AIS-B injuries (107). More recently, the E-STAND trial by Darrow proved that, even in the absence of prior dedicated neurorehabilitation, SCS can elicit immediate voluntary motor control in individuals with chronic thoracic AIS-A injuries, alongside improvements in autonomic function (239). Activation of SCS has immediate effects on motor function, enabling individuals with SCI to voluntarily recruit previously paralyzed muscles, even in the absence of prior training. However, these effects are transient and cease when the stimulation is turned off. For this reason, given its facilitating role, the stimulation protocol should be combined with intensive task-specific rehabilitation in order to obtain long-term benefits resulting from activity-dependent plasticity of the residual neural circuits (221). Collectively, these results have established SCS as a promising neurorestorative intervention for SCI, prompting extensive research efforts that have repeatedly demonstrated consistent and reproducible efficacy in facilitating motor recovery (236,240,241).

2. Background and Aim of the Study

Spinal cord injury (SCI) is a leading cause of severe and persistent motor disability in young adults, resulting in immediate and often permanent motor, sensory, and autonomic dysfunction below the level of the lesion, which ultimately lead to long-term disability and a reduced quality of life (QOF) (16). Among the various impairments arising from the SCI, the motor function recovery, particularly the standing and the gait ability, remains a primary therapeutic goal in individuals with paraplegia. Motor deficits represent one of the most disabling sequelae. Their development reflects both the loss of descending motor control and a series of secondary peripheral changes, including muscle atrophy and progressive reductions in muscle strength resulting from prolonged inactivity (68,69). Despite major advances in the management of acute complications and in rehabilitation approaches, no clinically established intervention is currently able to reliably restore lost motor function after the spinal damage (242,243). In recent years, SCS has emerged as a promising neuromodulatory approach capable of re-engaging dormant spinal networks and facilitating motor output in individuals with severe SCI (210).

Originally developed and approved for the management of chronic neuropathic pain (NP), commercially available SCS systems have been increasingly investigated for their potential to modulate spinal excitability and support voluntary motor control when applied below the level of injury (107,239). These systems were not specifically designed for motor rehabilitation, unlike highly specialized experimental platforms developed in preclinical and translational research settings. While previous studies have demonstrated the ability of SCS to enable standing and stepping movements in selected experimental cohorts, these investigations have largely been conducted under highly controlled conditions, often involving small sample sizes, short-term assessments, and customized stimulation system not directly translatable to routine clinical practice (244). Consequently, the long-term effects of clinically and off-the-shelf available stimulation devices on motor recovery and functional independence continue to be insufficiently characterized. Although, early evidence suggests that SCS can facilitate voluntary movements by increasing the excitability of spinal locomotor circuits and enhancing the integration of residual descending inputs, the extent to which these effects translate into durable functional improvements in real-world clinical populations is still unclear (219,245–247). Specifically, data related to long-term outcomes, sustainability of motor gains, and impact on QOF are currently limited.

The present prospective longitudinal trial was designed to address this gap by systematically evaluating the effects of SCS, delivered via clinically available systems, on motor recovery including a larger sample of individuals with chronic SCI. Specifically, this investigation aims to

assess the capacity of SCS devices to promote meaningful and sustained improvements in voluntary motor function over time, as well as to determine their impact on functional independence and QOF in a real-world clinical setting.

3. Materials and Methods

3.1 Experimental model and study participants details

The present study reports the results of a prospective clinical feasibility trial parsing the effect of SCS, combined with rehabilitation, on motor recovery in 10 patients with paraplegia and chronic NP following traumatic SCI (ClinicalTrials.gov ID: NCT05926843). The participants signed a written consent before their enrolment. The study was approved by IRCCS Ospedale San Raffaele ethical committee (protocol approved in October 2022, project ID: Neuro-SCS-001) and it was carried out in accordance with the Declaration of Helsinki. All the surgical and experimental procedures were performed at IRCCS Ospedale San Raffaele and Vita-Salute San Raffaele University (Milan, Italy), in collaboration with the BioRobotics Institute and the Interdisciplinary Health Science Research Center of Scuola Superiore Sant'Anna (Pisa, Italy). Participants selection was based on the following eligibility criteria.

Inclusion Criteria:

- Diagnosis of SCI from at least one-year post injury;
- Complete or incomplete spinal cord damage (classified as AIS A, AIS B or AIS C) conditioning chronic NP;
- Age > 18 years old;
- Indication to SCS surgery for chronic pain;
- Be unable to stand or step independently;
- No current anti-spasticity medication regimen;
- No botox injections in the prior 3 months.

Exclusion Criteria:

- Any person unable to lie still within the environment of the MRI scanner for the required period to perform the study and those where MRI scanning is contraindicated (metal clips, claustrophobia);
- Pregnancy or breastfeeding;
- Any significant psychiatric disease;
- Use of illicit drugs;
- Unstable medical condition, cardiopulmonary disease or dysautonomia that would contraindicate standing or stepping;
- Painful musculoskeletal dysfunction, unhealed fracture, contractures, pressure sores, or urinary tract infections that might interfere with stand or step training.

Patients P01, P02, P03 and P04 presented with incomplete motor injury (AIS C), while the patients P05, P06, P07, P08, P09 and P10 had motor complete injury (AIS A/AIS B). In addition, all participants were affected by NP spread to the lower limbs. Eventually, all patients suffered from neurogenic bladder and bowel dysfunction, requiring respectively intermittent self-catheterization and bowel irrigation.

Notably, patient P03 showed extensive LMN involvement in addition to the central SCI. Neurophysiological assessments revealed near-complete peripheral axonal and neuronal damage affecting the spinal roots and anterior horn from L4 to S1, coupled with mild persistent signs of acute denervation, as indicated by the presence of fibrillation potentials. Furthermore, chronic but incomplete axonal damage was observed bilaterally in the muscles innervated by the L2-L3 spinal roots/anterior horn. No fasciculations, cramps, or other involuntary movements were detected in the lower limbs.

All patients were actively engaged in regular physiotherapy programs prior to the trial admissions. The following tables provide an overview of the baseline demographic characteristics, injury-related parameters and corresponding MRI findings of all study participants.

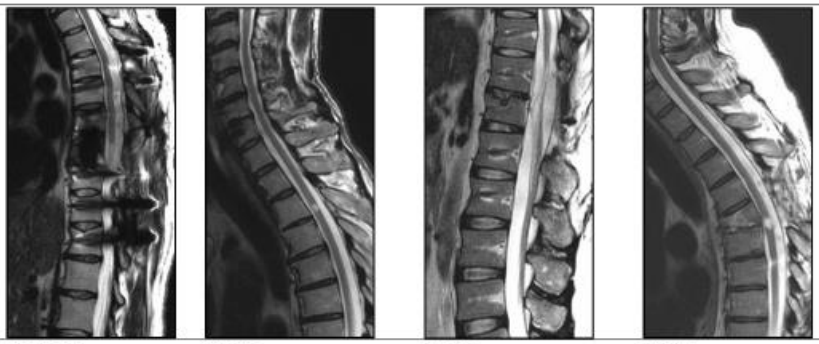
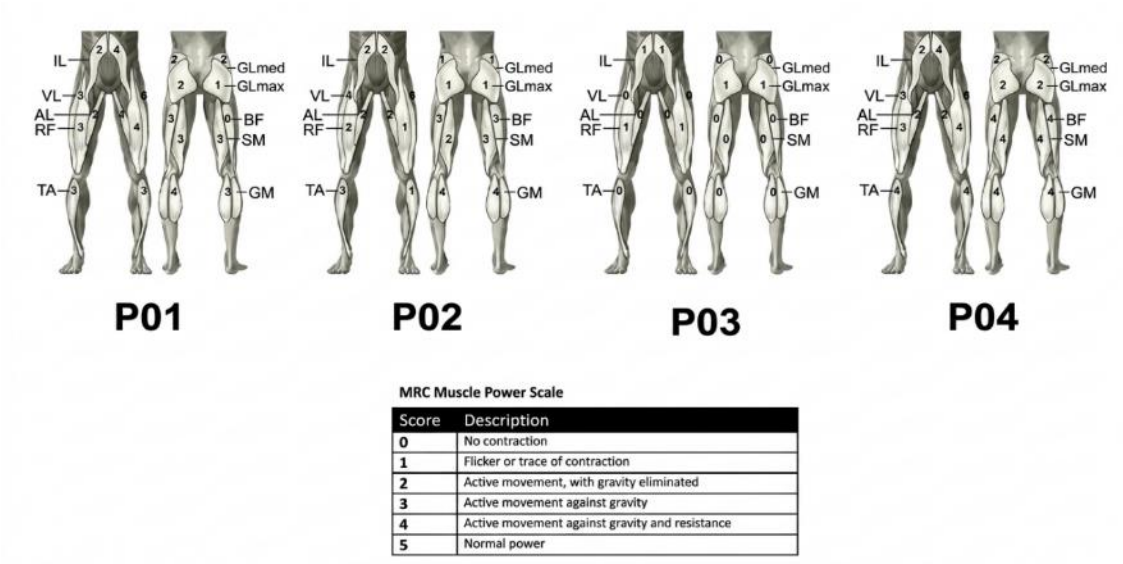
	P01	P02	P03	P04
MRI image				
Sex	Female	Male	Male	Male
Age (years)	32	55	32	50
Level of injury	T8	T3	T11	T6
Time from injury (months)	19	35	49	26
AIS grade	C	C	C	C

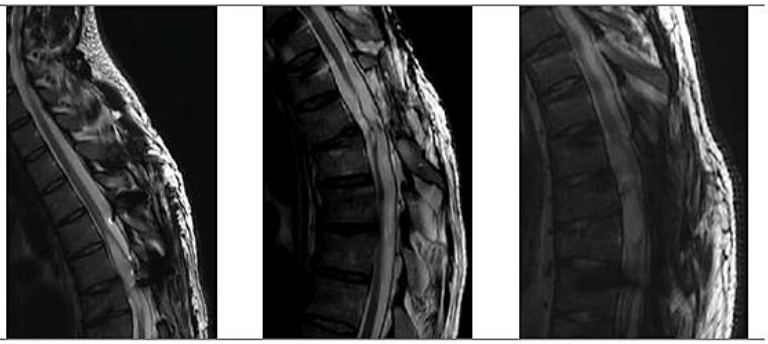
Table 7: Baseline characteristics of motor-incomplete patients (P01-P04) enrolled in the Neuro-SCS-001 trial.

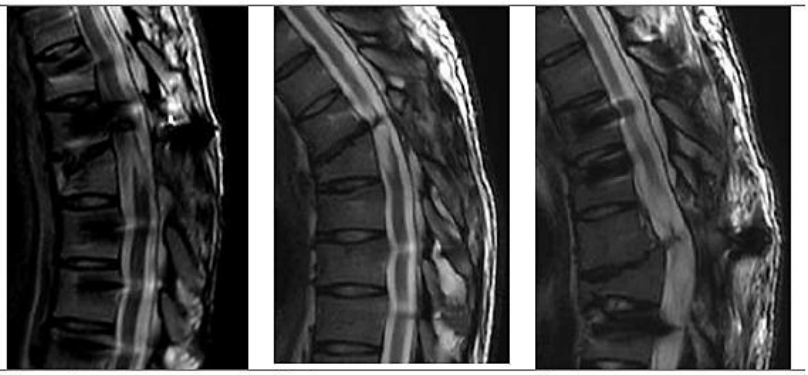


MRC Muscle Power Scale

Score	Description
0	No contraction
1	Flicker or trace of contraction
2	Active movement, with gravity eliminated
3	Active movement against gravity
4	Active movement against gravity and resistance
5	Normal power

Figure 26: Clinical assessment of residual muscle strength in incomplete motor patients (P01-P04). The table explain the MRC scale used to evaluate muscle strength grade.
Muscle abbreviations: IL: Iliopsoas, VL: Vastus Lateralis, AL: Adductor Longus, RF; Rectus Femoris, TA: Tibialis Anterior, GLmed: Gluteus Medius, GLmax: Gluteus Maximus, BF: Biceps Femoris; SM: Semimembranosus, GM: Gastrocnemius.

	P05	P06	P07
MRI image			
Sex	Male	Male	Male
Age (years)	27	33	18
Level of injury	T7	T4	T7
Time from injury (months)	32	36	12
AIS grade	B	A	B

	P08	P09	P10
MRI image			
Sex	Female	Male	Male
Age (years)	31	37	31
Level of injury	T6	T5	T6
Time from injury (months)	14	18	68
AIS grade	A	B	A

Tables 8-9: Baseline characteristics of motor-complete patients (P05-P10) enrolled in the Neuro-SCS-001 trial.

3.2 Neurorehabilitation protocol

The study was conducted in several sequential phases, beginning with comprehensive preoperative clinical, neurophysiological, neuroimaging, and neuropsychological evaluations. Following baseline assessments, participants underwent surgical implantation of the SCS system. After surgery, an initial phase for stimulation parameters tuning was carried out to identify the most effective stimulation set-up, followed by a structured inpatient rehabilitation program lasting at least 8 weeks.

During hospitalization, rehabilitation initially focused on reducing lower-limb hypertonia through stretching exercises targeting the ankle plantar flexors and knee extensors, facilitating residual isolated movements, and promoting upright standing and body-weight–supported walking. Once optimal low-frequency SCS (LF-SCS) configurations for selective muscle recruitment had been identified (chapter 3.4.2), training progressed to task-specific exercises involving both single- and multi-joint movements performed under stimulation in different postural conditions, including hip and knee flexion, as well as ankle dorsiflexion. These activities were supported by augmented feedback provided through Virtual Reality and wearable inertial sensors (Virtual Reality Rehabilitation System, VRRS; Khymeia S.R.L.) to enhance sensorimotor integration and task-oriented repetition.

Balance and postural control were subsequently trained under static standing conditions on different support surfaces, both with and without upper-limb assistance. Gait rehabilitation was started using a self-paced omnidirectional treadmill with real-time visual feedback (MoonWalker; Khymeia SRL), initially with full body-weight support and then progressively reducing assistance to zero until independent weight bearing was achieved. Patients then transitioned to overground walking practice with the aid of assistive devices when required, including walkers, crutches, and ankle–foot orthoses.

Notably, participant P03 required customized knee–ankle–foot orthoses to achieve and maintain an upright standing position.

During the inpatient stay, rehabilitation was delivered for approximately 15 hours per week. Upon discharge, rehabilitation continued through a home-based program supported by a dedicated virtual reality platform (VRRS Home-Kit; Khymeia SRL), which enabled remote monitoring of training adherence and performance. Exercise execution was continuously tracked, while physiotherapists provided regular supervision and adjustments.

The participants attended monthly follow-up visits for clinical evaluation and intensive one-day gait training sessions. Comprehensive multidisciplinary assessments were subsequently performed at the 6-month follow-up to estimate functional outcomes and the long-term effects of the intervention.

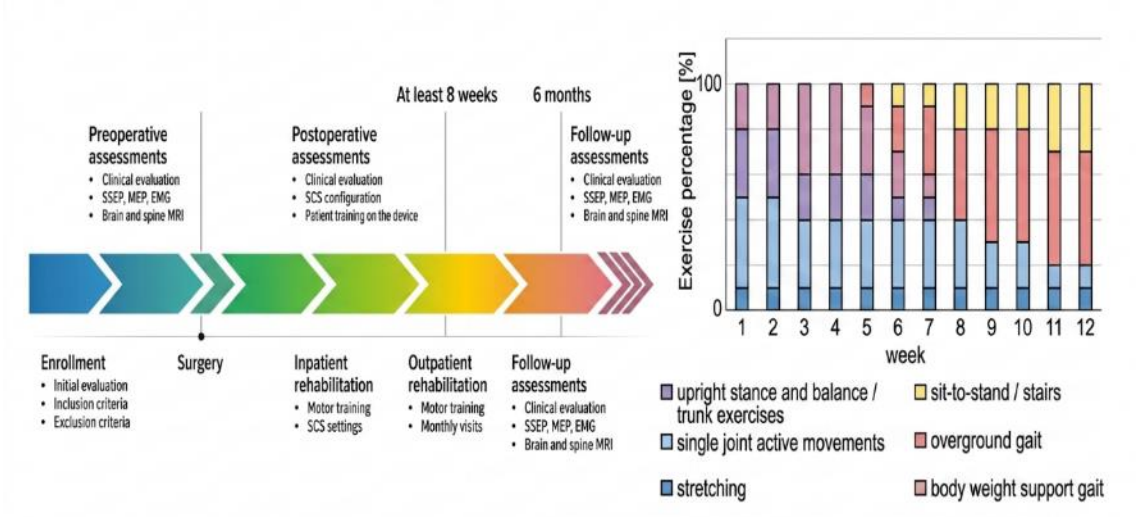


Figure 27: Left: Trial timeline phases and longitudinal rehabilitation protocol. Right: Stacked bar chart that shows the different percentage of sessions training time dedicated to specific task, highlighting the progressive shift from stretching and single joint movements to trunk exercises, body weight support and overground gait.

3.3 Neurosurgical procedure

After enrolment and completion of the preoperative evaluations, eligible participants underwent neurosurgical implantation of the SCS system. The surgical procedure comprised several consecutive phases: lumbar laminectomy, paddle lead insertion, and implantation of an internal pulse generator (IPG) under general anaesthesia.

Once the patient had been placed in the prone position, intraoperative fluoroscopy (Artis Pheno Robotic C-arm Angiography system, Siemens Healthineers GmbH, Erlangen, Germany) was used to accurately define the spinal anatomical landmarks, confirm the target levels, and guide the surgical procedure approach.

A midline skin incision centered on the L1 lamina was made, followed by the muscle fascia dissection and bilateral retraction of the paraspinal muscles in order to expose the posterior spinal structures. Subsequently, T12-L1 laminectomy was performed to remove the ligaments at the midline and expose the underlying dura mater accordingly. Subsequently, a 67-mm epidural paddle lead equipped with 32 contacts spaced 3 mm apart (CoverEdge X 32 lead, Boston Scientific Spa, Marlborough, USA) was carefully introduced into the epidural space. The lead was positioned along the spinal midline and advanced rostrally to the target location at T11–T12 intervertebral disc level. This configuration was selected to enable recruitment of trunk musculature, including the abdominal and erector spinae muscles, through stimulation delivered by the most rostral electrode contacts.

Following the lead implantation, single SCS pulses (2Hz) at increasing amplitudes was systematically delivered through the electrode contacts. Evoked motor responses were recorded

using the NeuroExplorer 2019 intraoperative monitoring system, with signals acquired by the subdermal or intramuscular electrodes placed in target muscle groups. This procedure enabled intraoperative mapping of muscle recruitment and optimization of lead positioning according to the desired stimulation profile.

Once the neurophysiological evaluation was completed, the paddle was secured using anchors suture to the surrounding ligaments and a final X-ray fluoroscopy was acquired to confirm the leads positioning.

Eventually, the paddle array cables were tunnelled subcutaneously and connected to the IPG (WaveWriter Alpha 32, Boston Scientific Spa, Marlborough, USA). The IPG was then implanted in a surgically created subcutaneous pocket within the abdominal wall.

3.4. SCS protocols

3.4.1 Single-pulse SCS

Following neurosurgical intervention, the first step of rehabilitation focused on characterizing muscle recruitment patterns elicited by SCS and assessing the selectivity of different electrodes configurations. To this end, single stimulation pulses were delivered through various anode–cathode arrangements using a pulse width of 300 μs and a frequency of 2 Hz, corresponding to the lowest frequency supported by the stimulation system. Stimulation amplitude was progressively increased, starting below the patient's sensory threshold and progressing until the motor response saturation or the onset discomfort, whichever occurred first, using increments of 0.1 mA and approximately ten pulses per amplitude level. Simultaneously, EMG activity was recorded from selected lower-limb muscles to generate motor recruitment curves.

These recruitment profiles were subsequently harnessed to identify stimulation setup capable of selectively activating specific muscle groups and to develop individualized stimulation protocols for isolated movements (including hip flexion, abdominal muscle activation, and trunk stabilization) and as well for walking.

To further enhance the spatial selectivity of stimulation across medio-lateral and rostro-caudal spinal regions, multiple multipolar electrodes configurations were systematically developed and tested during the training sessions.

Walking was achieved by concurrently activating the electrodes associated with trunk stability and hip flexion. Stimulation settings were then progressively optimized through an iterative process based on clinical observations and patient feedback until the final therapeutic configurations were defined. Throughout the rehabilitation period, stimulation amplitudes were adjusted daily. During tasks execution, SCS was continuously administered at intensity levels

modulated based on the patient's posture and maintained below the motor threshold, thereby facilitating voluntary muscle activation to contribute to the movement when desired.

3.4.2 Low Frequencies Spinal Cord Stimulation (LF-SCS)

To enhance single- and multi-joint movements, for each task the electrode configuration that most selectively recruited agonist muscles was selected, based on single-pulse SCS recruitment profiles. Continuous LF-SCS was subsequently delivered using this configuration, while systematically optimizing stimulation parameters, including amplitude and frequency. During stimulation, participants were instructed to attempt or execute the motor task repetitively and to provide qualitative feedback regarding perceived facilitation or interference. The pulse width was held constant at 300 µs for all experiments duration. Stimulation frequency was initially set at 40 Hz, while amplitude was progressively increased from the sensory threshold to the level eliciting involuntary muscle contractions, with incremental steps of approximately 1 mA.

Once the amplitude producing the best movement quality and optimal patient-reported facilitation was identified, it was kept constant while frequency was consistently varied from 20 to 100 Hz in 10 Hz increments. Throughout this tuning procedure, the EMG activity was recorded from selected lower-limb muscles, together with joint kinematics when voluntary movement could not be completed without SCS, or force output when task execution was possible in the absence of stimulation. The electrophysiological and biomechanical measurements collected were used to define the final LF-SCS protocols for both single- and multi-joint movements. Motor and sensory thresholds, and consequently the effective amplitude range, changed according to body posture and spinal curvature, in agreement with previous reports (248).

3.4.3 High Frequencies Spinal Cord Stimulation (HF-SCS)

To suppress undesired muscle contractions, a HF-SCS protocol was implemented using a stimulation frequency of 1.2 kHz and a pulse width of 20 µs, corresponding to the maximum frequency and minimum pulse width achievable with the stimulation device (160). For each type of task, stimulation amplitude was individually adjusted according to patient tolerance, and it was found to be significantly related to body posture. Consistent with previous findings, the sensory threshold was higher for HF-SCS than for LF-SCS (respectively 18 mA versus 6 mA during standing), suggesting distinct activation characteristics between the two stimulation protocols (249).

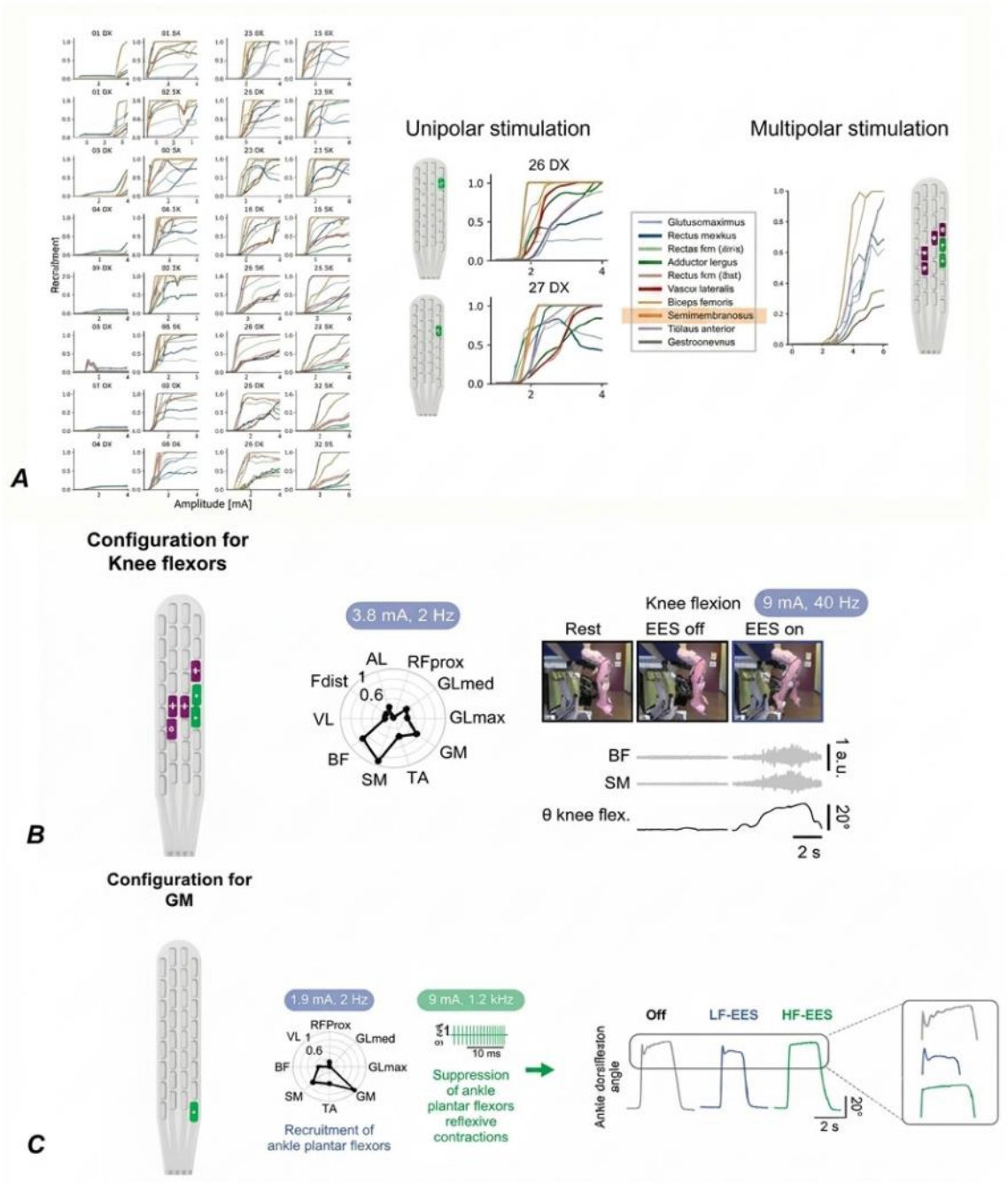


Figure 28: The different SCS protocols used in the Neuro-SCS-001 trial.
(A) *<u>Left:</u> muscle recruitment curves with the 2Hz single-pulse SCS. <u>Right:</u> unipolar vs multipolar stimulation. The unipolar stimulation is related with an insufficient specificity due to simultaneous muscle activation. Conversely, the multipolar stimulation increases the specificity, promoting a selective recruitment of the Semimembranosus (orange trace) through an optimized electrode configuration.*
(B)*The LF-SCS protocols recruit the main leg muscles, improving voluntary isolated movements (configuration for knee flexors).*
(C) *The HF-SCS protocols suppress the spastic muscle contractions (ankle plantar flexor reflexive contractions).*

3.5 Outcome measures and longitudinal evaluation

The motor function, spasticity, pain, and QOF outcomes were longitudinally measured to demonstrate the effects of SCS combined with rehabilitation. Motor function and spasticity were assessed by an experienced neurosurgeon and a physiotherapist respectively at the trial entry, at discharge (3 months after the enrolment) and then at 6 months from the admission.
Motor recovery was further characterized by documenting the earliest emergence of predefined functional motor benchmarks during active SCS, which included:

- **Muscle contraction**, defined as a visible or electromyographically detectable activation of the target muscle without external assistance.
- **Single-joint movement**, corresponding to the active movement through the available ROM, against gravity or with gravity eliminated depending on residual strength.
- **Standing**, which refers to the ability to maintain an upright posture with full weight bearing on both lower limbs, without external body-weight support.
- **Treadmill walking**, described as the ability to ambulate for 8 consecutive minutes on a treadmill (MoonWalker, Khymeia) at a constant speed (0,3 m/s) using a safety harness without body-weight support. The duration of the exercise was carefully selected to allow the task to be completed with limited fatigue.
- **Overground walking** assessed using standardized walking tests, specifically the 10-Meter Walk Test (10MWT) and the 6-Minute Walk Test (6MWT), already discussed in chapter 1.5.1.4 (78,79,81).

In addition, the assessment extended to the measurements of muscle strength (MRC scale) and spasticity (MAS). A detailed overview of MRC scale is reported below, whereas the MAS has been previously described in the chapter 1.5.4.4 (150,151).
The Medical Research Council (MRC) scale consists of six different grades:

- 0: no contraction;
- 1: flicker or trace of contraction;
- 2: active movement with gravity removed;
- 3: active movement against gravity;
- 4: active movement against gravity and resistance;
- 5: normal muscle strength.

In muscle groups with an MRC grade exceeding 2, isometric strength was further assessed using a handheld dynamometer (NOD, OT Bioelettronica). During testing to ensure reliable

measurements, the physiotherapist maintained the dynamometer stabilization to guarantee isometric contraction conditions, while participant positioning was standardized in accordance with MRC assessment guidelines for the corresponding muscle group.

Instead, pain was rated at baseline and 6 months after the trial admission through the Numerical Rating Scale (NRS) (161,250) and the Pain Catastrophizing Scale (PCS) (251), providing complementary measures of pain intensity and its cognitive-emotional burden.

Health-related QOF was gauged at study entry and at 6 months after surgery using the 36-Item Short Form Health Survey (SF-36), administered by an expert neuropsychologist (252).

Finally, adjustments in antispastic and analgesic therapies were prospectively monitored during follow-up, providing an additional measure to evaluate the clinical impact of the SCS protocol.

3.6 EMG and kinematic measurements

Muscle activity was recorded by surface EMG using the Sessantaquattro+ system (OT Bioelettronica), with sensors applied bilaterally to the major lower limb muscles involved in the stimulation targets, particularly the vastus lateralis (VL) and gastrocnemius medialis (GM).

In patient P02 it was not possible to acquire EMG signal from some muscles, respectively the adductor longus (AL) and the distal rectus femoris (RF).

The electrodes were placed on the skin surface avoiding the motor points, in order to reduce artefacts and ensure high-quality signal acquisition. In parallel, the kinematics of the lower limbs and trunk were detected by Inertial Measurements Units (IMUs, MTw Awinda Xsens) positioned on the feet, tibiae, femurs and sternum. The IMUs were oriented according to a standardized anatomical reference system, with cranially directed x-axis and anteriorly directed z-axis. Notably, the foot-mounted sensors were fixed to the dorsum of the foot.

This setup allowed the simultaneous recording of muscle activity and segmental movement during the experimental protocols.

3.7 Statistical analysis

Comparison between stimulation-on and stimulation-off conditions were performed using a one-way unpaired Kruskal–Wallis test. This non-parametric approach was applied to evaluate differences across experimental conditions when appropriate. Longitudinal changes in continuous variables were assessed using paired t-tests, comparing repeated measurements within the same participants over time. Statistical significance was set at $P < 0,05$ (or Bonferroni-corrected $P < 0,05$ where applicable).

4. Results

4.1 Spinal Cord Stimulation-associated functional outcomes

Functional outcomes were observed across all baselines AIS grades while SCS was active (AIS A, n = 3; AIS B, n = 3; AIS C, n = 4). Muscle contraction and single-joint movements emerged in all participants within the first post-surgery week (AIS A: 3/3; AIS B: 3/3; AIS C: 4/4). Standing ability was achieved by all patients (AIS A: 3/3; AIS B: 3/3; AIS C: 4/4) with mean times of 4.00 weeks in AIS A (range 2-7), 3.67 weeks in AIS B (range 3-5) and 2.00 weeks in AIS C. Progressive locomotor improvements were also consistently documented throughout the cohort. All AIS C participants (4/4) were able to perform treadmill walking, defined as 8 minutes of walking at 0.3 m/s using a safety harness without body-weight support, within an average of 3,75 weeks (range 3-4). Some individuals AIS A (2/3) and AIS B (2/3) transitioned directly to overground walking without undergoing a prior treadmill walking phase. Furthermore, all participants (AIS A: 3/3; AIS B: 3/3; AIS C: 4/4) successfully completed overground walking assessed at self-selected speed (with a walker as needed) using the 10-Meters Walking Test (10MWT) and the 6-Minutes Walking Test (6MWT) independently of injury severity.

Functional outcome	Reported with SCS on (n of patients)			Week of observation after surgery SCS on (mean, range)		
	AIS A	AIS B	AIS C	AIS A	AIS B	AIS C
Voluntary muscle contraction	3/3	3/3	4/4	1 (1)	1 (1)	1 (1)
Single joint movement	3/3	3/3	4/4	1 (1)	1 (1)	1 (1)
Standing	3/3	3/3	4/4	4 (2-7)	3,67 (3-5)	2 (2)
Treadmill walking	1/1*	1/1*	4/4	3 (3)	3 (3)	3,75 (3-4)
Overground walking	3/3	3/3	4/4	6 (4-9)	4,67 (3-6)	7,75 (5-11)

*Figure 29: Earliest occurrence of predefined functional motor outcomes recorder when the SCS was active, stratified by baseline AIS grades (AIS A, n = 3; AIS B, n = 3; AIS C, n = 4). In the first column, values are reported as the number of participants out of the total achieving each task, while in the second column as week of observation after surgery (mean and range). * Some patients, respectively 2 AIS B and 2 AIS A, transitioned directly to overground walking.*

4.2 Spinal cord stimulation and rehabilitation improved muscle strength

4.2.1 Motor-incomplete patients

In patients with incomplete motor SCI (P01–P04), SCS combined with rehabilitation was associated with both stimulation-dependent and stimulation-independent improvements in lower-limb muscle strength over the 6-month follow-up period. Muscle strength increased progressively from baseline and persist even in the absence of stimulation, suggesting recovery-related mechanisms mediated by spared descending pathways and/or detour circuits.

To enhance motor performance during standing and gait-related activities, single-pulse SCS was individually configured to preferentially target the weak proximal muscles on the most compromised side.

Quantitative dynamometric assessments revealed significant longitudinal changes in lower-limb strength. Data were unavailable for P03 because all evaluated muscles underscored MRC grade 3, and stimulation-ON measurements were not acquired for P01.

Overall, strength values increased over time across participants, with the most pronounced gains observed in proximal muscle groups involved in postural control and locomotion (hip flexors, knee extensors, and plantar flexors).

Although some muscle groups exhibited a modest reduction in strength at the 6-month follow-up compared with previous time points evaluations, their values remained higher than baseline levels. Finally, activation of stimulation during the 6-month assessment produced additional increases in force output in selected muscles.

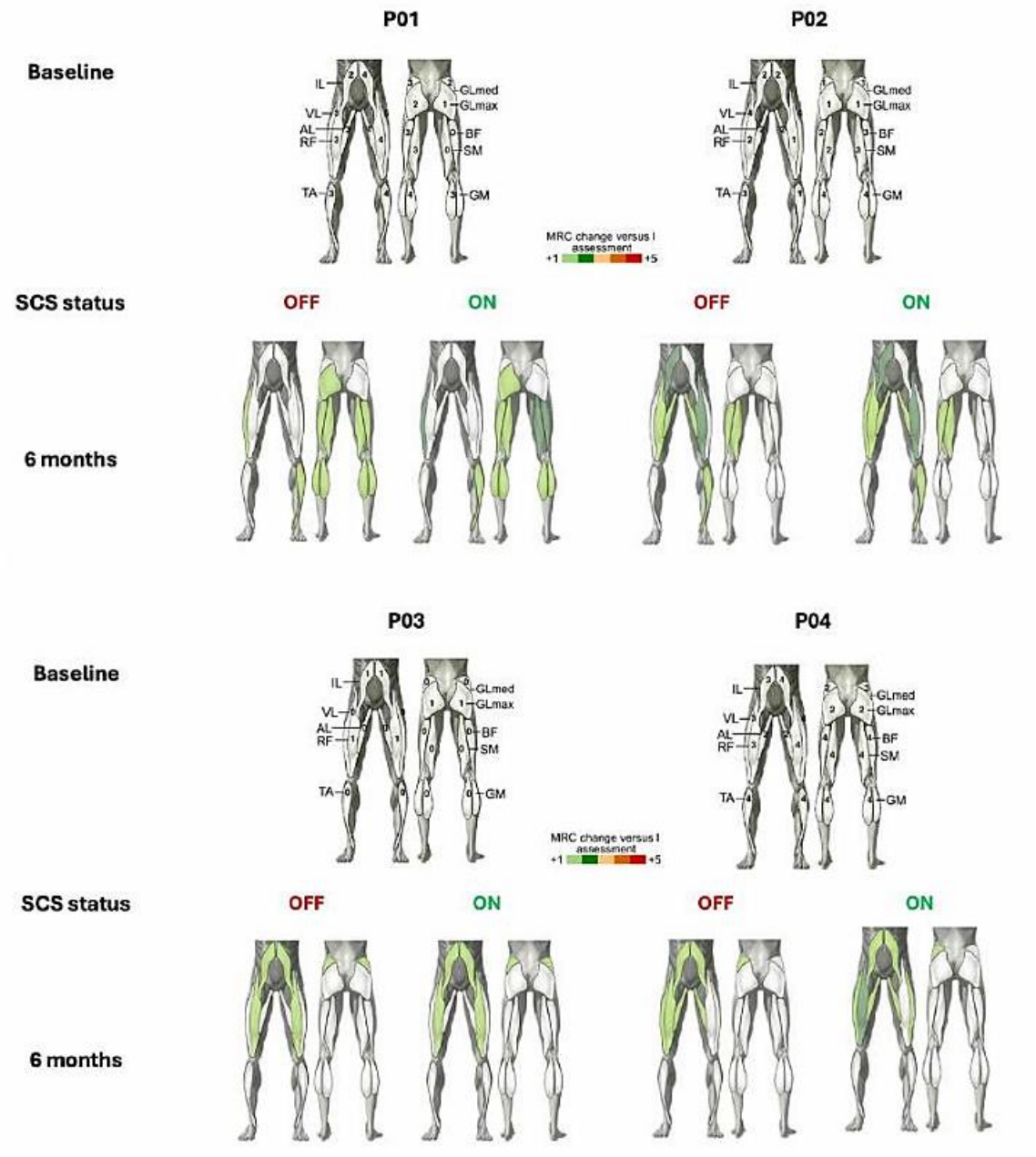


Figure 30: Schematic representation of muscular strength improvements in motor-incomplete patients (P01-P04). Upper panels: Baseline assessment. Lower panels: status at 6-month follow-up with stimulation condition OFF and ON. The muscle group targets were the hip flexors and knee extensors in order to optimize postural control and locomotor function.
P01: right VL reached MRC 5 (+1 vs OFF), while right BF and SM reached MRC 2 (+1 vs OFF).
P02: right VL reached MRC 5 (+1 vs OFF).
P03: no stimulation-dependent changes.
P04: left VL reached MRC 5 (+1 vs OFF) and right RF reached MRC 5 (+1 vs OFF).
Muscle abbreviations: IL: Iliopsoas, VL: Vastus Lateralis, AL: Adductor Longus, RF: Rectus Femoris, TA: Tibialis Anterior, GLmed: Gluteus Medius, GLmax: Gluteus Maximus, BF: Biceps Femoris, SM: Semimembranosus, GM: Gastrocnemius Medialis.

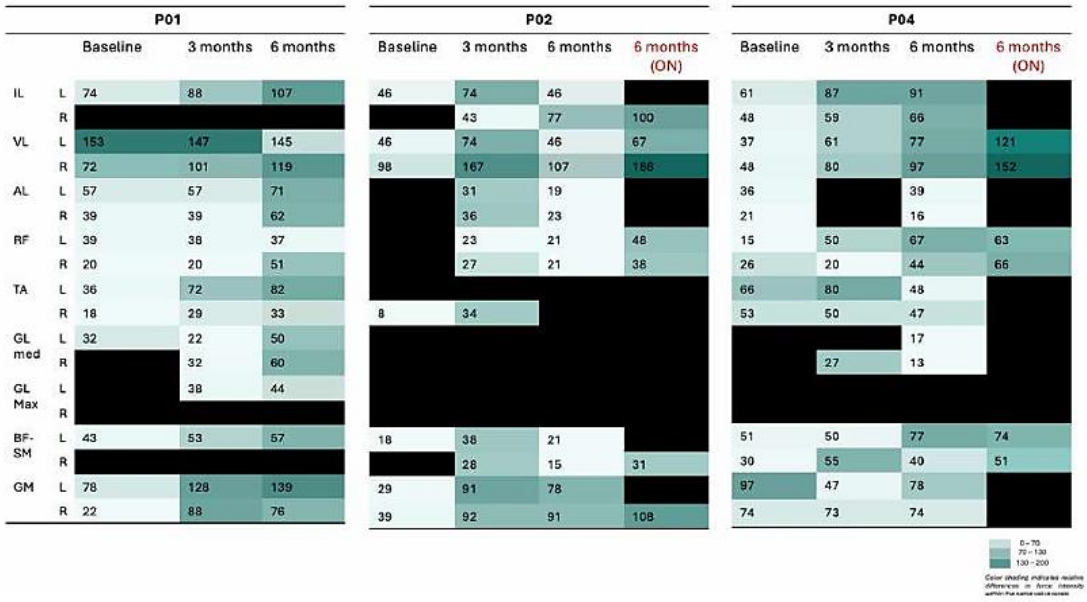


Figure 31: Heat maps illustrate maximal isometric force values (in Newtons). Colour intensity reflects relative force magnitude for each muscle group (darker teal indicates higher force). Black boxes refer to muscle groups for which data were not acquired because muscle strength was below grade 2 on the MRC scale.
Muscle abbreviations: IL: Iliopsoas, VL: Vastus Lateralis, AL: Adductor Longus, RF: Rectus Femoris, TA: Tibialis Anterior, GLmed: Gluteus Medius, GLmax: Gluteus Maximus, BF: Biceps Femoris, SM: Semimembranosus, GM: Gastrocnemius Medialis.
L: left, R: right.

4.2.2 Motor-complete patients

At baseline, all patients with motor-complete SCI (P05–P10) exhibited complete paralysis of the lower extremities, with an MRC score of 0 across all evaluated muscle groups. The single-pulse SCS protocol was specifically configured to preferentially recruit proximal hip flexors (iliopsoas) and knee extensors (vastus lateralis and rectus femoris), due to their key contribution to sagittal-plane stability during standing and the initiation of gait. Following stimulation onset, a consistent improvement in MRC scores was observed across the cohort. However, these effects were entirely stimulation-dependent, as muscle strength returned immediately to baseline levels (MRC 0) when stimulation was discontinued.

Quantitative dynamometric assessments corroborated the observed trends obtained through MRC evaluation. No voluntary muscle strength was detected at baseline or during any stimulation-OFF conditions, with all assessed muscle groups remaining at MRC grade 0, consistent with chronic motor-complete paralysis. Conversely, stimulation-ON evaluations revealed a substantia increases in force output within the targeted proximal muscle groups, specifically the iliopsoas and rectus femoris.

Peak force production was generally recorded at the 3-month assessment. Although a slight decline was detected at 6 months follow-up, values remained markedly higher than the baseline.

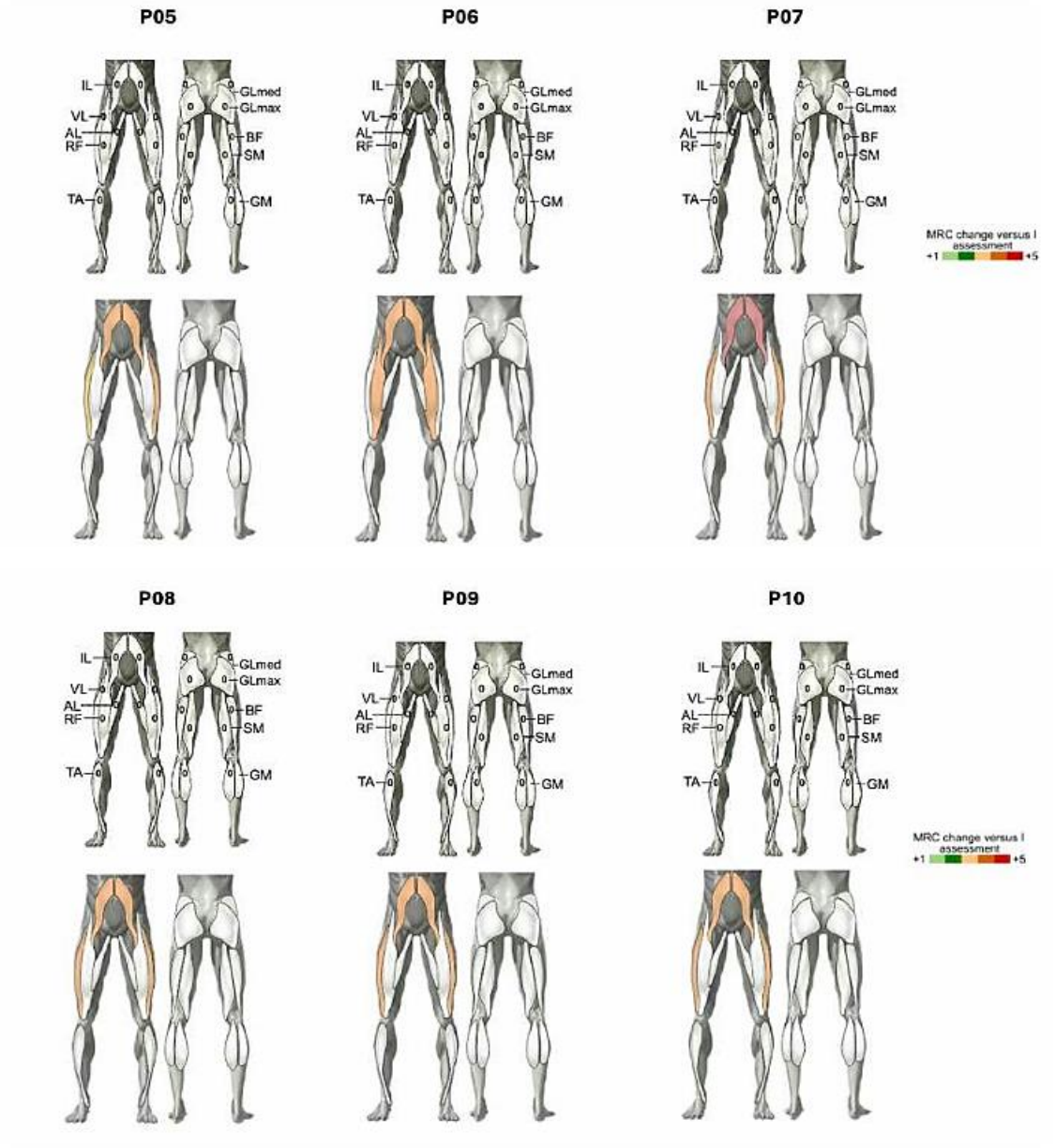
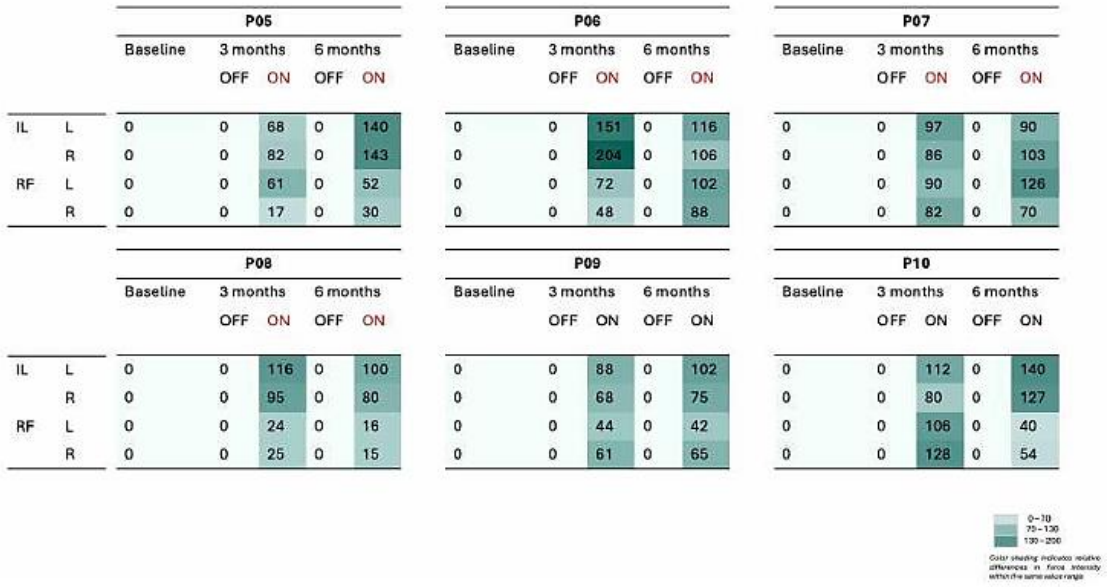


Figure 32: Schematic representation of muscular strength improvements in motor complete patients (P05-P10). Upper panels: Baseline assessment showing complete paralysis. Lower panels: status at 6-month follow-up in ON stimulation conditions. The muscle group targets were the hip flexors and knee extensors in order to optimize postural control and walking functions. Stimulation-OFF conditions are not shown, as they were identical to baseline and no muscle contraction was observed.
Muscle abbreviations: IL: Iliopsoas, VL: Vastus Lateralis, AL: Adductor Longus, RF: Rectus Femoris, TA: Tibialis Anterior, GLmed: Gluteus Medius, GLmax: Gluteus Maximus, BF: Biceps Femoris, SM: Semimembranosus, GM: Gastrocnemius Medialis.



		P05				
		Baseline	3 months		6 months	
			OFF	ON	OFF	ON
IL	L	0	0	68	0	140
	R	0	0	82	0	143
RF	L	0	0	61	0	52
	R	0	0	17	0	30

		P06				
		Baseline	3 months		6 months	
			OFF	ON	OFF	ON
IL	L	0	0	151	0	116
	R	0	0	204	0	106
RF	L	0	0	72	0	102
	R	0	0	48	0	88

		P07				
		Baseline	3 months		6 months	
			OFF	ON	OFF	ON
IL	L	0	0	97	0	90
	R	0	0	86	0	103
RF	L	0	0	90	0	126
	R	0	0	82	0	70

		P08				
		Baseline	3 months		6 months	
			OFF	ON	OFF	ON
IL	L	0	0	116	0	100
	R	0	0	95	0	80
RF	L	0	0	24	0	16
	R	0	0	25	0	15

		P09				
		Baseline	3 months		6 months	
			OFF	ON	OFF	ON
IL	L	0	0	88	0	102
	R	0	0	68	0	75
RF	L	0	0	44	0	42
	R	0	0	61	0	65

		P10				
		Baseline	3 months		6 months	
			OFF	ON	OFF	ON
IL	L	0	0	112	0	140
	R	0	0	80	0	127
RF	L	0	0	106	0	40
	R	0	0	128	0	54

Figure 33: Heat maps illustrate maximal isometric force values (in Newtons). Colour intensity reflects relative force magnitude for each muscle group (darker teal indicates higher force).
Muscles abbreviations: IL (Iliopsoas), RF (Rectus Femoris).
L: left, R: right.

4.3 Spinal cord stimulation and rehabilitation allow overground walking

4.3.1 Longitudinal assessment of overground walking facilitated by SCS

Locomotor recovery was assessed longitudinally by performing the 10MWT and the 6MWT. All participants achieved overground walking during the study period. Performance on the 10MWT improved longitudinally across the cohort. From the first measurable walking assessments (9.4 ± 4.1 weeks after implantation) to hospital discharge, all patients showed a progressive reduction in completion time (mixed-effects linear model, $P < 0.001$). These improvements remained evident at the six-month follow-up with respect to the first measurable time point (mixed-effects linear model, $P < 0.001$). All participants completed the 6MWT at least once during inpatient rehabilitation.

4.3.2 Motor-incomplete patients

Motor-incomplete participants increased covered distance by 43 ± 21 meters between the first measurable time point (10.8 ± 4.3 weeks) and hospital discharge with gains maintained at six-month follow-up (45 ± 25 meters increase versus first measurable assessment).

4.3.3 Motor-complete patients

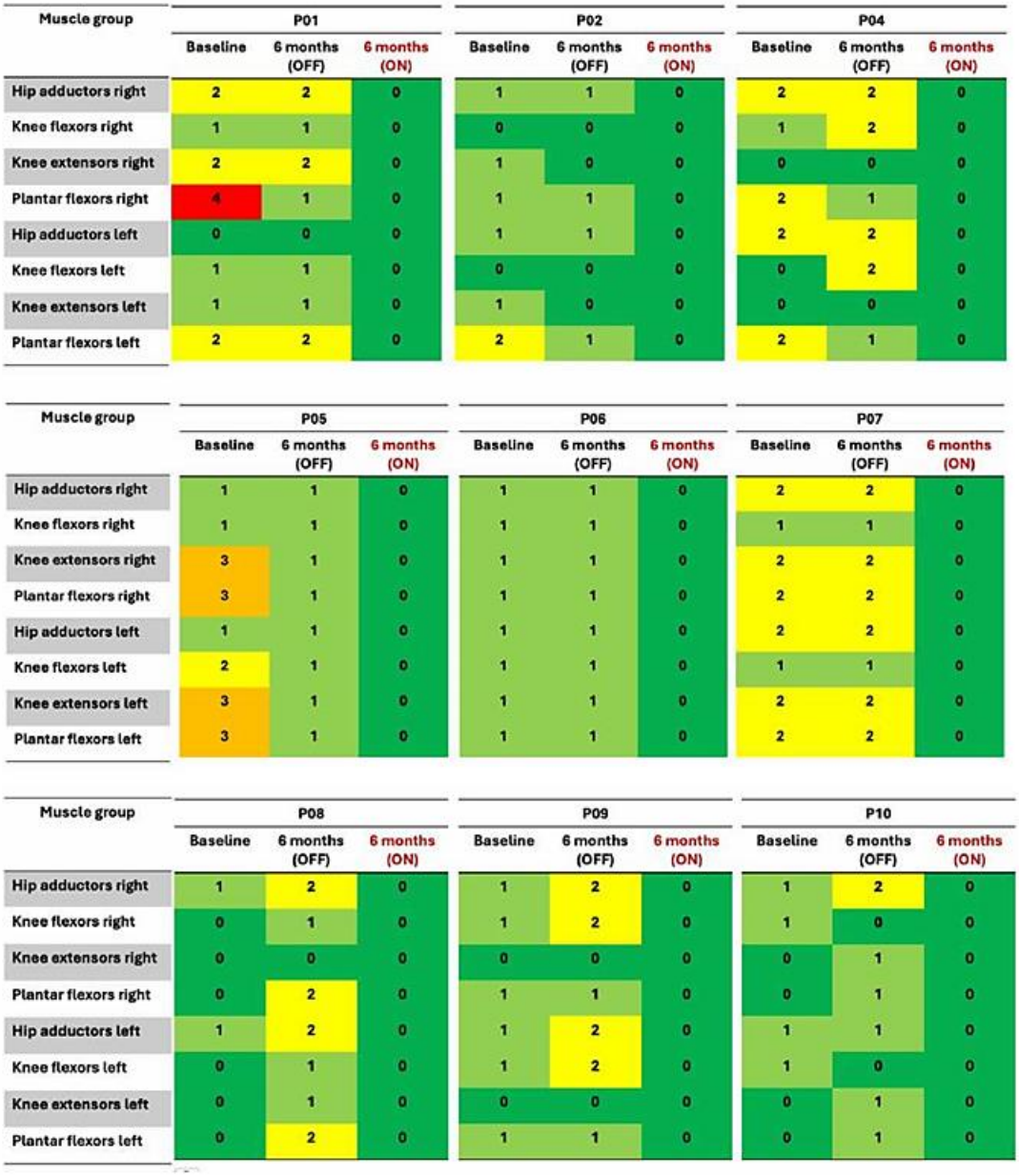
Motor-complete participants also achieved sustained overground walking during SCS. Participant P05 completed the 6MWT at hospital discharge and at six months, participant P06 completed the test once during inpatient rehabilitation, and participants P07 to P10 completed the assessment multiple times, including at hospital discharge and at the 6-month follow-up. Furthermore, participants from P08 to P10 showed progressive increases in covered walking distance between the first measurable time point and both the assessment at hospital discharge and at the 6-month follow-up. To evaluate endurance during stimulation-dependent motor tasks, we additionally assessed prolonged standing and walking capacity in motor-complete participants. Standing duration increased longitudinally in the ON condition (Wilcoxon signed-rank test, $P = 0.03$), so that all participants except P06 were able to maintain continuous standing for more than 30 min at discharge. Regarding walking endurance, all motor-complete participants were able to walk for more than 6 minutes with stimulation ON, with two patients (P08 and P10) surpassing a 100-meter walking distance.

4.4 Spinal cord stimulation and rehabilitation improve spasticity

Spasticity was evaluated using the Modified Ashworth Scale (MAS) during follow-up assessments performed under both stimulation-OFF and stimulation-ON conditions. Patient P03 was excluded from this analysis due to concomitant central and peripheral nerve injury, which resulted in flaccid muscle tone at baseline, precluding MAS evaluation. During active HF-SCS, spasticity was completely abolished (MAS = 0) across all assessed muscle groups in both motor-incomplete and motor-complete cohorts. Notably, this response was observed irrespective of baseline spasticity severity, demonstrating a consistent and immediate inhibitory effect of neuromodulation on abnormal reflex-mediated muscle activity.

In the motor-incomplete cohort (P01, P02, P04), muscle tone showed a favourable longitudinal evolution. At the 6-month follow-up under stimulation-OFF conditions, spasticity was stable or reduced in most muscle groups, with the most pronounced improvements observed in postural agonists. Furthermore, distal postural antagonist muscles exposed to repetitive loading during gait training demonstrated marked reductions in tone (plantar flexors in P01, MAS 4 → 1). A localized increase in knee flexor spasticity was recorded in P04, reflecting the compensatory overactivity of antagonist muscle groups during intensive standing exercises.

In contrast, the motor-complete cohort (P05–P10) exhibited a more heterogeneous and overall, less favourable progression of spasticity under stimulation-OFF conditions at 6 months follow-up. In most participants (P06–P10), spasticity persisted or increased across a greater number of muscle groups compared with baseline, particularly in proximal and distal postural muscles. This pattern is consistent with heightened spinal excitability in the absence of effective supraspinal modulation. Patient P05 constituted a notable exception, showing a generalized reduction in spasticity across all evaluated muscle groups at the 6-month OFF assessment.



Muscle group	P01			P02			P04		
	Baseline	6 months (OFF)	6 months (ON)	Baseline	6 months (OFF)	6 months (ON)	Baseline	6 months (OFF)	6 months (ON)
Hip adductors right	2	2	0	1	1	0	2	2	0
Knee flexors right	1	1	0	0	0	0	1	2	0
Knee extensors right	2	2	0	1	0	0	0	0	0
Plantar flexors right	4	1	0	1	1	0	2	1	0
Hip adductors left	0	0	0	1	1	0	2	2	0
Knee flexors left	1	1	0	0	0	0	0	2	0
Knee extensors left	1	1	0	1	0	0	0	0	0
Plantar flexors left	2	2	0	2	1	0	2	1	0

Muscle group	P05			P06			P07		
	Baseline	6 months (OFF)	6 months (ON)	Baseline	6 months (OFF)	6 months (ON)	Baseline	6 months (OFF)	6 months (ON)
Hip adductors right	1	1	0	1	1	0	2	2	0
Knee flexors right	1	1	0	1	1	0	1	1	0
Knee extensors right	3	1	0	1	1	0	2	2	0
Plantar flexors right	3	1	0	1	1	0	2	2	0
Hip adductors left	1	1	0	1	1	0	2	2	0
Knee flexors left	2	1	0	1	1	0	1	1	0
Knee extensors left	3	1	0	1	1	0	2	2	0
Plantar flexors left	3	1	0	1	1	0	2	2	0

Muscle group	P08			P09			P10		
	Baseline	6 months (OFF)	6 months (ON)	Baseline	6 months (OFF)	6 months (ON)	Baseline	6 months (OFF)	6 months (ON)
Hip adductors right	1	2	0	1	2	0	1	2	0
Knee flexors right	0	1	0	1	2	0	1	0	0
Knee extensors right	0	0	0	0	0	0	0	1	0
Plantar flexors right	0	2	0	1	1	0	0	1	0
Hip adductors left	1	2	0	1	2	0	1	1	0
Knee flexors left	0	1	0	1	2	0	1	0	0
Knee extensors left	0	1	0	0	0	0	0	1	0
Plantar flexors left	0	2	0	1	1	0	0	1	0

Figure 34: Longitudinal assessment of muscle spasticity using the Modified Ashworth Scale (MAS) in motor-incomplete (P01, P02, P04) and motor-complete (P05–P10) patients of Neuro-SCS-001 trial. For each subject, MAS scores are reported at baseline and at 6 months follow-up with both in OFF and ON conditions. Activation of the HF-SCS protocol resulted in complete suppression of spasticity (MAS = 0) across all evaluated muscle groups in all participants.

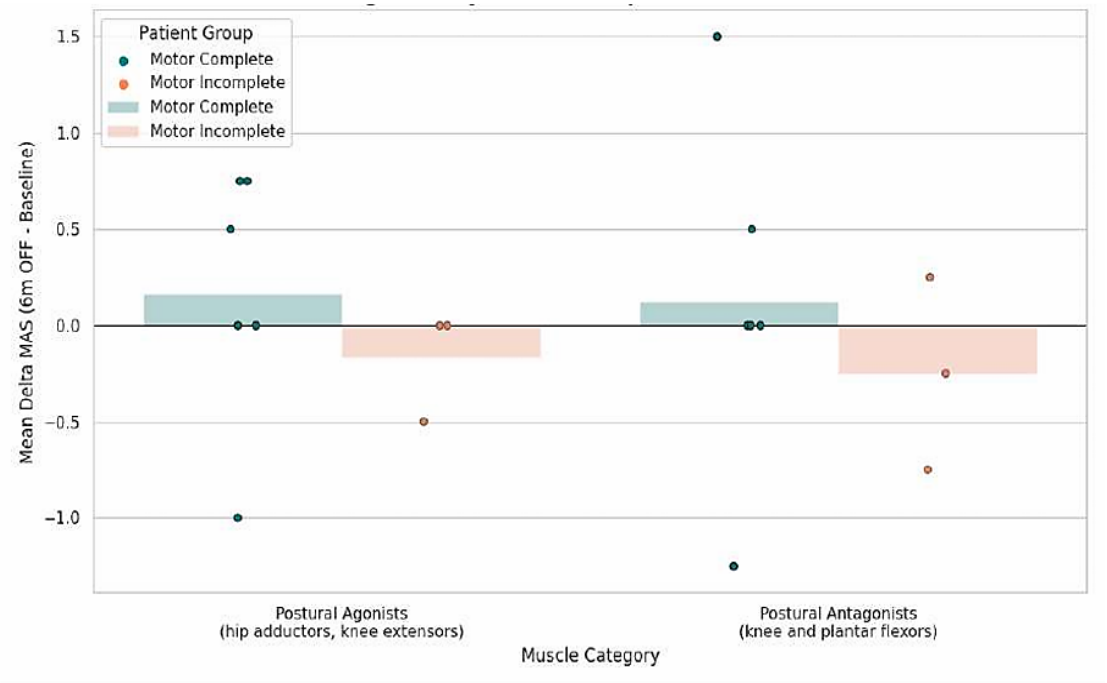


Figure 35: The bar and swarm plots illustrate the variation in muscle tone (Delta MAS: 6-month follow-up OFF-Baseline) across the postural agonist (hip adductors, knee extensors) and the postural antagonist (knee flexors, plantar flexors).

5. Discussion

5.1 Data interpretation

The present study demonstrates that SCS combined with rehabilitation promotes substantial recovery of motor function in patients with paraplegia following SCI. Although the mechanism and degree of recovery differ between complete and incomplete injuries, improvements were observed in muscle strength, standing ability, locomotor performance, and spasticity modulation, highlighting the capacity of SCS to elicit both immediate stimulation-dependent effects and longer-term neuroplastic adaptations.

5.1.1 Motor outcomes

During SCS protocol, all AIS subgroups achieved early motor endpoints, including voluntary contraction and isolated joint movements within the 1st week, progression to standing at approximately 2–4 weeks, and overground walking at around 5–8 weeks (mean onset: AIS A = 6.0 weeks, AIS B = 4.67 weeks, AIS C = 7.75 weeks).

Motor outcomes, assessed with the Medical Research Council (MRC) scale, improved in both motor-complete and motor-incomplete participants mainly in the proximal muscles group required for standing. Stimulation parameters were customized based on the individual clinical profile of each patient, prioritizing the side exhibiting greater clinical impairment when relevant. Among motor-incomplete patients, motor scores at the 6-month follow-up remained significantly higher than the baseline, even under OFF stimulation conditions. The persistence of these gains suggests a durable therapeutic effect rather than a transient neuromodulatory response. These findings are consistent with activity-dependent neuroplastic mechanisms promoted by the combined SCS protocol and intensive rehabilitation. Such mechanisms may facilitate the functional recruitment of spared descending pathways and the formation of detour circuits, ultimately leading to sustained improvements in volitional motor control (184).

In motor-complete patients a consistent increase in motor output was observed, however these effects were stimulation-dependent with muscle strength returning to baseline levels upon cessation of SCS activity. No voluntary motor activity was detected in OFF conditions at any time point. This strict ON/OFF dissociation suggests that the observed motor output was not driven by restored voluntary descending control, but rather by a state-dependent facilitation of spinal motor networks. Notably, SCS increases the excitability of lumbosacral spinal networks through the recruitment of large-diameter proprioceptive afferents, thereby facilitating sensorimotor integration within spinal intraneuronal circuits and residual central pattern-generating (CPG) networks that remain functionally silent following complete SCI (184).

Across cohorts, quantitative force measures tended to peak during the inpatient period and to partially reduce at 6-month follow-up. This non-linear trajectory remarks the synergistic nature of SCS and rehabilitation, suggesting that SCS alone is not sufficient to drive optimal functional gains: while stimulation provides a permissive physiological state for recruitment, the magnitude and persistence of gains remain dependent on the intensity and quality of task-specific practice. The transition to home-based rehabilitation likely resulted in a reduction in training intensity, suggesting that part of the observed functional gains was use-dependent. This emphasizes the need for scalable post-discharge strategies to sustain rehabilitation intensity and promoting long-term functional improvements.

The ability of all participants to achieve overground walking represents a clinically relevant outcome, particularly the fact that the 6MWT could be performed by all individuals during the inpatient rehabilitation proves the early emergence of endurance-related capacity with the combined intervention. The progressive reduction in the 10MWT completion time from the first measurable walking assessment to hospital discharge, together with its persistence at six months, suggests that recovery was not limited to an early adaptive phase but was consolidated over time. Motor-incomplete participants demonstrated meaningful improvements in walking distance that persisted at the six-month follow-up, even in absence of active stimulation. This pattern is consistent with the contribution of residual supraspinal pathways, which may be progressively reinforced through repeated task-specific training facilitated by SCS.

Motor-complete participants achieved sustained overground walking under ON-stimulation conditions, with several individuals exhibiting progressive increases in walking distance across successive assessments. While these gains remained strictly dependent on stimulation, the concomitant improvement in standing and walking endurance suggests an enhanced capacity of lumbosacral networks to support prolonged motor output, likely as a result of repeated neuromodulatory activation during SCS protocol.

Overall, these findings support a dual interpretation of recovery: in motor-incomplete patients, SCS may interact with preserved descending pathways to promote long-term neuroplastic changes, whereas in motor-complete patients it primarily acts as a state-dependent technology revealing latent spinal locomotor circuits under appropriate neuromodulatory circumstances.

5.1.2 Spasticity suppression

Spasticity was evaluated using the Modified Ashworth Scale (MAS). We investigated whether HF-SCS could attenuate spastic co-contraction and thereby facilitate the movement.

HF-SCS protocols were individually tailored and delivered at 1.2 kHz, with stimulation amplitude set at the maximum tolerated level, in line with evidence suggesting that kilohertz-frequency conduction block is more effective at higher intensities (253,254). During the ON-state, a

complete suppression of spasticity was recorded across all evaluated muscle groups, with MAS scores reduced to 0 in both motor-incomplete and motor-complete participants. This effect was consistently observed regardless of baseline spasticity severity, indicating a robust and reproducible acute inhibitory action on overactive spinal reflex circuits.

In contrast, the OFF-stimulation conditions revealed a severity-dependent rebound in spasticity, reflecting the reversible nature of high-frequency conduction block. In motor-incomplete individuals, spasticity remained stable or showed slight improvement over time, whereas in motor-complete individuals tended to persist or increase. Notably, participants P06–P10 exhibited greater increases in muscle tone, especially in proximal and distal postural muscle groups. This pattern may indicate a heightened sub-lesional excitability without supraspinal modulation, potentially amplified by intensive inpatient exposure to single-pulse/LF-SCS and locomotor training.

5.2 Literature review

Recent advances in SCS have shifted the field from non-specific tonic drive toward biomimetic stimulation guided by Spatio-Temporal Activation Rules (STAR). Traditional tonic SCS, as reported by Angeli et al. (107) and Gill et al. (255), increases spinal excitability globally, enabling residual sensory input and any preserved descending signals to be transformed into motor output. However, this approach relies on spinal self-organization and typically requires months of high-intensity training to achieve functional stepping. In contrast, the STAR paradigm, introduced by Wagner et al. (219) and further refined by Rowald et al. (244) delivers phase-synchronized, spatiotemporally patterned sequences mimicking the physiological motor-pool recruitment. By synchronizing stimulation with the gait cycle, this form of targeted neurotechnology helps preserve proprioceptive feedback and can facilitate the rapid emergence of stepping and walking. This conceptual shift is supported by mechanistic evidence from Danner et al. (256) who demonstrated that the functionally isolated human lumbosacral SC contains modular burst-generating networks capable of producing rhythmic, multi-muscle activation patterns in response to SCS.

Consistently, our findings indicate that STAR-based stimulation reduces the time required to achieve clinically meaningful locomotor outcomes, including overground walking, compressing the typical timeframe reported for tonic-drive paradigms from several months to only a few weeks (Table 10).

These results were obtained using a standard 32 contact commercial paddle lead (CoverEdge X), in contrast to the customized high-density arrays employed in multiple STAR studies. This

indicates that STAR protocols can be effectively conducted with commercially available hardware, thereby enhancing feasibility and facilitating broader clinical translation. Our data on neural plasticity in OFF conditions confirm a dichotomy based on the severity of the injury. In agreement with Angeli and Wagner (107,219), only patients with residual neurological sparing showed improvements in voluntary motor strength without active stimulation. Conversely, for motor-complete patients, our results validate the observations of Rowald et al. (244), supporting the concept that STAR acts as a necessary functional bypass, where locomotor output remains strictly dependent on device-driven activation.

The most significant innovation of the Neuro-SCS-001 trial is the active management of spasticity. In the existing literature, spasticity is frequently treated as a confounding variable or an obstacle addressed through intensive habituation (107). Similarly, mechanistic studies investigating spinal burst generators within the functionally isolated SC have mainly characterized motor output under epidural drive, without explicitly addressing pathological muscle tone (256). The clinical relevance of this strategy becomes evident when compared with current benchmarks. In their systematic review of 24 studies on spinal causes of spasticity (predominantly chronic post-traumatic SCI), Jung et al. reported that conventional tonic SCS, delivered at low frequencies (30–100 Hz), is typically associated with partial reductions in spasticity in the order of 1–2 points on the MAS (78% of patients, 56/72) (257). The same review highlights the challenge on spasticity–movement balance: reducing tone enough to facilitate locomotion while avoiding over-suppression that could blunt residual volitional drive or increase discomfort. Across our cohort (N = 10), HF-SCS alone achieved complete ON-state tone suppression on the MAS (MAS = 0 across evaluated muscle groups), with the reduction maintained even at the 6-month follow-up in incomplete patients; conversely, motor-complete patients exhibited a suppression of spasticity that was strictly stimulation-dependant.

Study	N / Injury Grade	Protocol Type	Motor Milestones (week range, % of patients)			Training Load
			Voluntary Contraction (ON)	*Standing (ON)*	*Overground Walking (ON)*	
Neuro-SCS-001	N=10; AIS A/B/C	Hybrid (Continuous + HF-EES)	1 (100%)	2–7 (100%)	4–11 (100%)	≥ 8 wks inpatient (15 h/wk) + VR home kit
Rowald et al. (2022)	N=3; AIS A	STAR	1 (100%)	1 (100%)	1 (100%)	~5 months; 4–5x/wk (1–3h sessions) STIMO model
Wagner et al. (2018)	N=3 AIS C/D	STAR	1 (100%)	1	1 (100%)	~5 months; 4–5x/wk (1–3h sessions) STIMO model
Angeli et al. (2018)	N=4; AIS A/B	Continuous EES	1 (100%)	1-10 (100%)	15–85 (50%)	81–278 sessions; 15–85 wks total
Gill et al. (2018)	N=1; AIS A	Continuous EES	1 (100%)	1–4 (100%)	43 (100%)	43 wks; 113 total sessions

Table 10: Comprehensive comparison of SCS protocols, motor milestones and training load. Functional motor outcomes are recorded under ON conditions.

5.3 Limitations

The present study is subject of several limitations inherent to feasibility design. The small sample size and the marked heterogeneity in baseline neurological impairments (AIS A-C) reduce the validity of these findings and may have contributed to inter-individual variability response to treatment. In addition, concomitant peripheral/orthopaedic constraints (particularly evident in P03), may acted as a confounding factor affecting functional performance. Milestone timing reflects the “earliest observation”; however, this could be influenced by rehabilitation scheduling and training intensity and therefore not be closely related to biological recovery. The lack of a

randomized control group or sham condition restricts the ability to establish a causal relationship between the intervention and the observed outcomes: potential contributions from rehabilitation, placebo effects, or spontaneous variability cannot be fully excluded.

Spasticity was assessed using clinical scales (MAS), which are susceptible to inter-rater variability and may not accurately detect the underlying neurophysiological mechanisms or long-term changes in spinal excitability. Furthermore, SCS protocols and rehabilitation were individualized, and stimulation settings were adapted over time. Even though this approach closely reflects real-world clinical practice, it may limit reproducibility across different centers without a standardized programming algorithm.

Finally, the relatively short follow-up duration of 6 months limits the assessment of long-term treatment durability an

Finally, the relatively short follow-up duration of six months limits the assessment of long-term clinical benefits durability.

These limitations restrict the strength of causal inferences and the generalizability of the outcomes; however, these results provide a coherent physiological and clinical rationale for larger controlled studies.

6. Conclusions

The Neuro-SCS-001 study is a prospective pilot trial designed to investigate the effects of the SCS combined with locomotor training in a cohort of 10 patients with paraplegia and spasticity following SCI. Overall, SCS protocol paired with a customized rehabilitation program resulted in clinically meaningful locomotor improvements across all participants, characterized by immediate stimulation-dependent effects and sustained functional improvements over time. Notably, motor-incomplete individuals also demonstrated stimulation-independent gains indicating the potential for enduring neurological recovery beyond the direct effects of device activation.

Concomitantly, HF-SCS lead to a powerful suppression of spasticity during ON states, independently of baseline injury severity. Despite the intensive delivery of standing and walking programs associated with high-dose locomotor training, during OFF conditions the assessments revealed that spasticity did not consistently decrease across participants. In fact, in a subset of patients the spasticity even augmented during the follow-up period, suggesting that repeated facilitation of spinal circuits may differentially modulate spinal excitability depending on injury severity and the degree of preserved descending control.

Taken together, these results provide a promising foundation for future research in neuromodulation and functional recovery after SCI.

7. References

1. Darby SA. General anatomy of the spinal cord. In: Cramer GD, Darby SA, editors. Clinical anatomy of the spine, spinal cord, and ANS. 3rd edn. Mosby; 2014. p. 65–97.

2. Williams PL, Warwick R, Dyson M, Bannister LH, editors. Gray's anatomy. 37th edn. Churchill Livingstone; 1989.

3. Rexed B. The cytoarchitectonic organization of the spinal cord in the cat. J Comp Neurol. 1952;96(3):414–95.

4. Rexed B. A cytoarchitectonic atlas of the spinal cord in the cat. J Comp Neurol. 1954;100(2):297–379.

5. W RR. Renshaw cell mediated inhibition of Renshaw cells: patterns of excitation and inhibition from impulses in motor axon collaterals. J Neurophysiol. 1970;33(2):257–70.

6. Kröger S, Watkins B. Muscle spindle function in healthy and diseased muscle. Skelet Muscle. 2021;11(1):3.

7. Zampieri N, Nooij JC. Regulating muscle spindle and Golgi tendon organ proprioceptor phenotypes. Curr Opin Physiol. 2021; 19:204–10.

8. Jankowska E, Roberts WJ. An electrophysiological demonstration of the axonal projections of single spinal interneurons in the cat. J Physiol. 1972;222(3):597–622.

9. Eccles RM, Lundberg A. Supraspinal control of interneurons mediating spinal reflexes. J Physiol. 1959;147(3):565–84.

10. Hultborn H, Udo M. Convergence in the reciprocal Ia inhibitory pathway of excitation from descending pathways and inhibition from motor axon collaterals. Acta Physiol Scand. 1972 Jan;84(1):95–108.

11. Crone C, Hultborn H, Jespersen B, Nielsen J. Reciprocal Ia inhibition between ankle flexors and extensors in man. J Physiol. 1987 Aug; 389:163–85.

12. Hongo T, Jankowska E, Lundberg A. The rubrospinal tract. II. Facilitation of interneuronal transmission in reflex paths to motoneurons. Exp Brain Res. 1969;7(4):365–91.

13. Gossard JP, Brownstone RM, Barajon I, Hultborn H. Transmission in a locomotor-related group Ib pathway from hindlimb extensor muscles in the cat. Exp Brain Res. 1994;98(2):213–28.

14. Hultborn H. Spinal reflexes, mechanisms and concepts: from Eccles to Lundberg and beyond. Prog Neurobiol. 2006;78(3–5):215–32.

15. McDonald JW, Sadowsky C. Spinal-cord injury. Lancet Lond Engl. 2002;359(9304):417–25.

16. O'Shea TM, Burda JE, Sofroniew MV. Cell biology of spinal cord injury and repair. J Clin Invest. 2017;127(9):3259–70.

17. Anjum A, Yazid MD, Fauzi Daud M, Idris J, Ng AMH, Selvi Naicker A, et al. Spinal Cord Injury: Pathophysiology, Multimolecular Interactions, and Underlying Recovery Mechanisms. Int J Mol Sci. 2020;21(20):7533.

18. Alizadeh A, Dyck SM, Karimi-Abdolrezaee S. Traumatic Spinal Cord Injury: An Overview of Pathophysiology, Models and Acute Injury Mechanisms. Front Neurol. 2019; 10:282.

19. Hawkins LA, Devitt A. Current understanding of the mechanisms for clearance of apoptotic cells-a fine balance.

20. Soderblom C, Luo X, Blumenthal E, Bray E, Lyapichev K, Ramos J, et al. Perivascular fibroblasts form the fibrotic scar after contusive spinal cord injury. J Neurosci. 2013 Aug;21;33(34):13882-7.

21. Bareyre FM, Kerschensteiner M, Raineteau O, Mettenleiter TC, Weinmann O, Schwab ME. The injured spinal cord spontaneously forms a new intraspinal circuit in adult rats. Nat Neurosci. 2004; Mar;7(3):269-77.

22. Park KK, Liu K, Hu Y, Smith PD, Wang C, Cai B, et al. Promoting axon regeneration in the adult CNS by modulation of the PTEN/mTOR pathway. Science. 2008 Nov;7;322(5903):963-6.

23. Liu K, Lu Y, Lee JK, Samara R, Willenberg R, Sears-Kraxberger I, et al. PTEN deletion enhances the regenerative ability of adult corticospinal neurons. Nat Neurosci. 2010; Sep;13(9):1075-81.

24. Sun F, Park KK, Belin S, Wang D, Lu T, Chen G, et al. Sustained axon regeneration induced by co-deletion of PTEN and SOCS3. Nature. 2011 Nov;6;480(7377):372-5.

25. Neumann S, Bradke F, Tessier-Lavigne M, Basbaum AI. Regeneration of sensory axons within the injured spinal cord induced by intraganglionic cAMP elevation. Neuron. 2002 Jun;13;34(6):885-93.

26. Anderson MA, Burda JE, Ren Y, Ao Y, O'Shea TM, Kawaguchi R, et al. Astrocyte scar formation aids central nervous system axon regeneration. Nature. 2016;14;532(7598):195-200.

27. Busch SA, Horn KP, Cuascut FX, Hawthorne AL, Bai L, Miller RH, et al. Adult NG2+ cells are permissive to neurite outgrowth and stabilize sensory axons during macrophage-induced axonal dieback after spinal cord injury. J Neurosci. 2010 Jan;6;30(1):255-65.

28. Hackett AR, Lee JK. Understanding the NG2 Glial Scar after Spinal Cord Injury. Front Neurol. 2016 Nov;7(199).

29. Jones LL, Sajed D, Tuszynski MH. Axonal regeneration through regions of chondroitin sulfate proteoglycan deposition after spinal cord injury: a balance of permissiveness and inhibition. J Neurosci. 2003 Oct;15;23(28):9276-88.

30. Cajal RY, Santiago, Defelipe J, Jones EG, May RM. Cajal's Degeneration and Regeneration of the Nervous System [Internet]. 2012.

31. Chemotropic guidance facilitates axonal regeneration and synapse formation after spinal cord injury. Nat Neurosci. 2009; Sep;12(9):1106-13.

32. Hollis ER. Axon Guidance Molecules and Neural Circuit Remodeling After Spinal Cord Injury. Neurotherapeutics. 2nd; Apr;13(2):360-9.

33. I FT, MM B, NJ A. The role of neuronal versus astrocyte-derived heparan sulfate proteoglycans in brain development and injury. Biochem Soc Trans. 2014; Oct;42(5):1263-9.

34. Lee JK, Chow R, Xie F, Chow SY, Tolentino KE, Zheng B. Combined genetic attenuation of myelin and semaphorin-mediated growth inhibition is insufficient to promote serotonergic axon regeneration. J Neurosci. 2010 Aug;11;30(32):10899-904.

35. Plantman S, Patarroyo M, Fried K, Domogatskaya A, Tryggvason K, Hammarberg H, et al. Integrin-laminin interactions controlling neurite outgrowth from adult DRG neurons in vitro. Mol Neurosci. 2008; Sep;39(1):50-62.

36. Hong S, Stevens B. Microglia: Phagocytosing to Clear, Sculpt, and Eliminate. Dev Cell. 2016 Jul;25;38(2):126-8.

37. Schwab ME, Strittmatter SM. Nogo limits neural plasticity and recovery from injury. Curr Opin Neurobiol. 2014; 27:53–60.

38. R GV, ME FV, M MF, A MM, Barrera S S. Update on traumatic acute spinal cord injury. Part 1. Med Intensiva. 2017.

39. Rupp R, Biering-Sørensen F, Burns SP, Graves DE, Guest J, Jones L, et al. International Standards for Neurological Classification of Spinal Cord Injury: Revised 2019. Top Spinal Cord Inj Rehabil. 2021; Spring;27(2):1-22

40. Henke AM, Billington ZJ, DR G Jr. Autonomic Dysfunction and Management after Spinal Cord Injury: A Narrative Review. J Med. 2022 Jul;7;12(7):1110.

41. Hagen EM. Acute complications of spinal cord injuries. World J Orthop. 2015 Jan;18;6(1):17-23.

42. Cryns N, Himmelhaus S, Irrgang S, Ernst M, Weidner N, Scheel-Sailer A. Acute Spinal Cord Injury guideline group. Clinical Practice Guideline: The Diagnosis and Treatment of AcuteSpinal Cord Injury. Dtsch Arztebl Int. 2025 Apr;18;122(8):219-224.

43. Wagner R, Jagoda A. Spinal cord syndromes. Emerg Med Clin North Am. 1997; Aug;15(3):699-711.

44. Diaz E, Morales H. Spinal Cord Anatomy and Clinical Syndromes. Semin Ultrasound CT MR. Epub. 2016; Oct;37(5):360-71.

45. SCHNEIDER RC, CHERRY G, PANTEK H. The syndrome of acute central cervical spinal cord injury; with special reference to the mechanisms involved in hyperextension injuries of cervical spine. J Neurosurg. 1954;(v;11(6):546-77).

46. Quinones C, JP W Jr, Kumbhare D, Guthikonda B, Hoang S. Clinical Assessment and Management of Acute Spinal Cord Injury. J Clin Med. 2024 Sep;25;13(19):5719.

47. Fehlings MG, Martin AR, Tetreault LA, Aarabi B, Anderson P, Arnold PM, et al. A Clinical Practice Guideline for the Management of Patients with Acute Spinal Cord Injury: Recommendations on the Role of Baseline Magnetic Resonance Imaging in Clinical Decision Making and Outcome Prediction. Glob Spine J. 2017; Sep;7(3 Suppl):221S-230S

48. Saragiotto BT, Maher CG, Lin CWC, Verhagen AP, Goergen S, Michaleff ZA. Canadian C-spine rule and the National Emergency X-Radiography Utilization Study (NEXUS) for detecting clinically important cervical spine injury following blunt trauma. Cochrane Database Syst Rev. 2018;11;2018(4):CD012989.

49. Kwan I, Bunn F, Roberts I. Spinal immobilisation for trauma patients. Cochrane Database Syst Rev. 2001;2001(2):002803.

50. Theodore N, Hadley MN, Aarabi B, Dhall SS, Gelb DE, Hurlbert RJ, et al. Prehospital cervical spinal immobilization after trauma. Neurosurgery. 2013;72 Suppl 2:22–34.

51. Ryken TC, Hurlbert RJ, Hadley MN, Aarabi B, Dhall SS, Gelb DE, et al. The acute cardiopulmonary management of patients with cervical spinal cord injuries. Neurosurgery. 2013;72 Suppl 2:84–92.

52. Vale FL, Burns J, Jackson AB, Hadley MN. Combined medical and surgical treatment after acute spinal cord injury: results of a prospective pilot study to assess the merits of aggressive medical resuscitation and blood pressure management. J Neurosurg. 1997;87(2):239–46.

53. Velmahos GC, Toutouzas K, Chan L, Tillou A, Rhee P, Murray J, et al. Intubation after cervical spinal cord injury: to be done selectively or routinely? Am Surg. 2003;69(10):891–4.

54. Khan M, Prabhakaran K, Jehan F, Anderson P, Con J, Lombardo G, et al. Early tracheostomy in patients with cervical spine injury reduces morbidity and improves resource utilization. Am J Surg. 2020;220(3):773–7.

55. Posluszny JA Jr, Onders R, Kerwin AJ, Weinstein MS, Stein DM, Knight J, et al. Multicenter review of diaphragm pacing in spinal cord injury: successful not only in weaning from ventilators but also in bridging to independent respiration. J Trauma Acute Care Surg. 2014;76(2):303–10.

56. Du JY, Shafi K, Blackburn CW, Chapman JR, Ahn NU, Marcus RE, et al. Resource Utilization Following Anterior Versus Posterior Cervical Decompression and Fusion for Acute Central Cord Syndrome. Clin Spine Surg. 2024;37(7):309–16.

57. Fehlings MG, Vaccaro A, Wilson JR, Singh A, Cadotte W, D. H, et al. Early versus delayed decompression for traumatic cervical spinal cord injury: results of the Surgical Timing in Acute Spinal Cord Injury Study (STASCIS. PloS One. 2012;7(2):32037.

58. B BM. Steroids for acute spinal cord injury. Cochrane Database Syst Rev. 2012;1(1):001046.

59. Bracken MB, Collins WF, Freeman DF, Shepard MJ, Wagner FW, Silten RM, et al. Efficacy of methylprednisolone in acute spinal cord injury. JAMA. 1984;251(1):45–52.

60. Vedantam A, Levi AD. Hypothermia for Acute Spinal Cord Injury. Neurosurg Clin N Am. 2021;32(3):377–87.

61. Grossman RG, Fehlings MG, Frankowski RF, Burau KD, Chow DS, Tator C, et al. A prospective, multicenter, phase I matched-comparison group trial of safety, pharmacokinetics, and preliminary efficacy of riluzole in patients with traumatic spinal cord injury. J Neurotrauma. 2014;31(3):239–55.

62. Walters BC, Hadley MN, Hurlbert RJ, Aarabi B, Dhall SS, Gelb DE, et al. American Association of Neurological Surgeons; Congress of Neurological Surgeons. Guidelines for the management of acute cervical spine and spinal cord injuries: 2013 update Neurosurgery 2013.

63. Guest J, Datta N, Jimsheleishvili G, Gater DR Jr. Pathophysiology, Classification and Comorbidities after Traumatic Spinal Cord Injury. J Pers Med. 2022;12(7):1126.

64. Burnside ER, Bradbury EJ. Manipulating the extracellular matrix and its role in brain and spinal cord plasticity and repair. Neuropathol Appl Neurobiol. 2014;40(1):26–59.

65. Debenham MIB, Franz CK, Berger MJ. Neuromuscular consequences of spinal cord injury: New mechanistic insights and clinical considerations. Muscle Nerve. 2024;70(1):12–27.

66. McComas AJ, Sica RE, Upton AR, Aguilera N. Functional changes in motoneurones of hemiparetic patients. J Neurol Neurosurg Psychiatry. 1973;36(2):183–93.

67. Xiong GX, Zhang JW, Hong Y, Guan Y, Guan H. Motor unit number estimation of the tibialis anterior muscle in spinal cord injury. Spinal Cord. 2008;46(10):696–702.

68. Hunter J, Ashby P. Secondary changes in segmental neurons below a spinal cord lesion in man. Arch Phys Med Rehabil. 1984;65(11):702–5.

69. K TC. Contractile properties of human thenar muscles paralyzed by spinal cord injury. Muscle Nerve. 1997;20(7):788–99.

70. W DL. Changes in motor innervation and cholinesterase localization induced by botulinum toxin in skeletal muscle of the mouse: differences between fast and slow muscles. J Neurol Neurosurg Psychiatry. 1970;33(1):40–54.

71. Lin KH, Chen YC, Luh JJ, Wang CH, Chang YJ. H-reflex, muscle voluntary activation level, and fatigue index of flexor carpi radialis in individuals with incomplete cervical cord injury. Neurorehabil Neural Repair. 2012;26(1):68–75.

72. Hiersemenzel LP, Curt A, Dietz V. From spinal shock to spasticity: neuronal adaptations to a spinal cord injury. Neurology. 2000;54(8):1574–82.

73. Faist M, Mazevet D, Dietz V, Pierrot-Deseilligny E. A quantitative assessment of presynaptic inhibition of Ia afferents in spastics. Differences in hemiplegics and paraplegics. Brain J Neurol. 1994;117(Pt 6):1449–55.

74. Calancie B, Molano MR, Broton JG. Tendon reflexes for predicting movement recovery after acute spinal cord injury in humans. Clin Neurophysiol Off J Int Fed Clin Neurophysiol. 2004;115(10):2350–63.

75. Ziu E, Weisbrod LJ, Mesfin FB. Spinal Shock. In: StatPearls. StatPearls Publishing; 2024.

76. Lam T, Noonan VK, Eng JJ, Team SCIRER. A systematic review of functional ambulation outcome measures in spinal cord injury. Spinal Cord. 2008;46(4):246–54.

77. Sinovas-Alonso I, Gil-Agudo Á, Cano-de-la-Cuerda R, Del-Ama AJ. Walking Ability Outcome Measures in Individuals with Spinal Cord Injury: A Systematic Review. Int J Environ Res Public Health. 2021;18(18):9517.

78. Hedel HJ, Wirz M, Dietz V. Standardized assessment of walking capacity after spinal cord injury: the European network approach. Neurol Res. 2008;30(1):61–73.

79. Jackson AB, Carnel CT, Ditunno JF, Read MS, Boninger ML, Schmeler MR, et al. Outcome measures for gait and ambulation in the spinal cord injury population. J Spinal Cord Med. 2008;31(5):487–99.

80. Graham JE, Ostir GV, Fisher SR, Ottenbacher KJ. Assessing walking speed in clinical research: a systematic review. J Eval Clin Pract. 2008;14(4):552–62.

81. Brooks D, Solway S, Gibbons WJ. ATS statement on six-minute walk test. Am J Respir Crit Care Med. 2003;167(9):1287.

82. Podsiadlo D, Richardson S. The timed 'Up & Go': a test of basic functional mobility for frail elderly persons. J Am Geriatr Soc. 1991;39(2):142–8.

83. Herbison GJ, Isaac Z, Cohen ME, Ditunno JF Jr. Strength post-spinal cord injury: myometer vs manual muscle test. Spinal Cord. 1996;34(9):543–8.

84. Schwartz S, Cohen ME, Herbison GJ, Shah A. Relationship between two measures of upper extremity strength: manual muscle test compared to hand-held myometry. Arch Phys Med Rehabil. 1992;73(11):1063–8.

85. Balbinot G, Li G, Wiest MJ, Pakosh M, Furlan JC, Kalsi-Ryan S, et al. Properties of the surface electromyogram following traumatic spinal cord injury: a scoping review. J Neuroengineering Rehabil. 2021;18(1):105.

86. Dietz V, Wirz M, Colombo G, Curt A. Locomotor capacity and recovery of spinal cord function in paraplegic patients: a clinical and electrophysiological evaluation. Electroencephalogr Clin Neurophysiol. 1998;109(2):140–53.

87. Thomas CK, Zaidner EY, Calancie B, Broton JG, Bigland-Ritchie BR. Muscle weakness, paralysis, and atrophy after human cervical spinal cord injury. Exp Neurol. 1997;148(2):414–23.

88. Calancie B, Molano MR, Broton JG. EMG for assessing the recovery of voluntary movement after acute spinal cord injury in man. Clin Neurophysiol Off J Int Fed Clin Neurophysiol. 2004;115(8):1748–59.

89. Pilkar R, Momeni K, Ramanujam A, Ravi M, Garbarini E, Forrest GF. Use of Surface EMG in Clinical Rehabilitation of Individuals With SCI: Barriers and Future Considerations. Front Neurol. 2020; 11:578559.

90. Petersen JA, Spiess M, Curt A, Dietz V, Schubert M, Group EMSCIS. Spinal cord injury: one-year evolution of motor-evoked potentials and recovery of leg motor function in 255 patients. Neurorehabil Neural Repair. 2012;26(8):939–48.

91. Curt A, Keck ME, Dietz V. Functional outcome following spinal cord injury: significance of motor-evoked potentials and ASIA scores. Arch Phys Med Rehabil. 1998;79(1):81–6.

92. Ahuja CS, Wilson JR, Nori S, Kotter MRN, Druschel C, Curt A, et al. Traumatic spinal cord injury. Nat Rev Dis Primer. 2017; 3:17018.

93. H DB. Motor rehabilitation after stroke, traumatic brain, and spinal cord injury: common denominators within recent clinical trials. Curr Opin Neurol. 2009;22(6):563–9.

94. Lam T, Eng JJ, Wolfe DL, Hsieh JT, Whittaker M, Team SR. A systematic review of the efficacy of gait rehabilitation strategies for spinal cord injury. Top Spinal Cord Inj Rehabil. 2007;13(1):32–57.

95. Behrman AL, Harkema SJ. Locomotor training after human spinal cord injury: a series of case studies. Phys Ther. 2000;80(7):688–700.

96. Holanda LJ, Silva PMM, Amorim TC, Lacerda MO, Simão CR, Morya E. Robotic assisted gait as a tool for rehabilitation of individuals with spinal cord injury: a systematic review. J Neuroengineering Rehabil. 2017;14(1):126.

97. Charbonneau R, Loyola-Sanchez A, McIntosh K, MacKean G, Ho C. Exoskeleton use in acute rehabilitation post spinal cord injury: A qualitative study exploring patients' experiences. J Spinal Cord Med. 2022;45(6):848–56.

98. Baunsgaard CB, Nissen UV, Brust AK, Frotzler A, Ribeill C, Kalke YB, et al. Exoskeleton gait training after spinal cord injury: An exploratory study on secondary health conditions. J Rehabil Med. 2018;50(9):806–13.

99. Mehrholz J, Kugler J, Pohl M. Locomotor training for walking after spinal cord injury. Cochrane Database Syst Rev. 2012;11(11):006676.

100. Marquez-Chin C, Popovic MR. Functional electrical stimulation therapy for restoration of motor function after spinal cord injury and stroke: a review. Biomed Eng Online. 2020;19(1):34.

101. Ho CH, Triolo RJ, Elias AL, Kilgore KL, DiMarco AF, Bogie K, et al. Functional electrical stimulation and spinal cord injury. Phys Med Rehabil Clin N Am. 2014;25(3):631-.

102. Kralj A, Bajd T, Turk R. Enhancement of gait restoration in spinal injured patients by functional electrical stimulation. Clin Orthop. 1988; 233:34–43.

103. Graupe D, Kohn KH. Functional neuromuscular stimulator for short-distance ambulation by certain thoracic-level spinal-cord-injured paraplegics. Surg Neurol. 1998;50(3):202–7.

104. Solomonow M, Baratta R, Hirokawa S, Rightor N, Walker W, Beaudette P, et al. The RGO Generation II: muscle stimulation powered orthosis as a practical walking system for thoracic paraplegics. Orthopedics. 1989;12(10):1309–15.

105. Andrews BJ, Baxendale RH, Barnett R, Phillips GF, Yamazaki T, Paul JP, et al. Hybrid FES orthosis incorporating closed loop control and sensory feedback. J Biomed Eng. 1988;10(2):189–95.

106. Kanakis AK, Benetos IS, Evangelopoulos DS, Vlamis J, Vasiliadis ES, Kotroni A, et al. Electrical Stimulation and Motor Function Rehabilitation in Spinal Cord Injury: A Systematic Review. Cureus. 2024;16(5):61436.

107. Angeli CA, Boakye M, Morton RA, Vogt J, Benton K, Chen Y, et al. Recovery of Over-Ground Walking after Chronic Motor Complete Spinal Cord Injury. N Engl J Med. 2018;379(13):1244–50.

108. Rossignol S, Dubuc R, Gossard JP. Dynamic sensorimotor interactions in locomotion. Physiol Rev. 2006;86(1):89–154.

109. Störmer S, Gerner HJ, Grüninger W, Metzmacher K, Föllinger S, Wienke C, et al. Chronic pain/dysaesthesiae in spinal cord injury patients: results of a multicentre study. Spinal Cord. 1997;35(7):446–55.

110. Finnerup NB, Gyldensted C, Fuglsang-Frederiksen A, Bach FW, Jensen TS. Sensory perception in complete spinal cord injury. Acta Neurol Scand. 2004;109(3):194–9.

111. L. PP Jr. Chapter 28. The clinical use of somatosensory evoked potentials in spinal cord injury. Clin Neurosurg. 1973; 20:367–81.

112. D'Angelo CM, Van Gilder JC, Taub A. Evoked cortical potentials in experimental spinal cord trauma. J Neurosurg. 1973 Mar;38(3):332–6.

113. Caizhong X, Chunlei S, Beibei L, Zhiqing D, Qinneng D, Tong W. The application of somatosensory evoked potentials in spinal cord injury rehabilitation. NeuroRehabilitation. 2014;35(4):835–40.

114. Curt A, Dietz V. Ambulatory capacity in spinal cord injury: significance of somatosensory evoked potentials and ASIA protocol in predicting outcome. Arch Phys Med Rehabil. 1997 Jan;78(1):39–43.

115. Shy ME, Frohman EM, So YT, Arezzo JC, Cornblath DR, Giuliani MJ, et al. Quantitative sensory testing: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology. 2003 Mar 25;60(6):898–904.

116. Krassioukov A, Wolfe DL, Hsieh JT, Hayes KC, Durham CE. Quantitative sensory testing in patients with incomplete spinal cord injury. Arch Phys Med Rehabil. 1999 Oct;80(10):1258–63.

117. Chang WK, Jung YS, Oh MK, Kim K. Quantitative Assessment of Proprioception Using Dynamometer in Incomplete Spinal Cord Injury Patients: A Preliminary Study. Ann Rehabil Med. 2017 Apr;41(2):218–24.

118. Dambreville C, Pairot de Fontenay B, Blanchette AK, Roy JS, Mercier C, Bouyer L. Ankle proprioception during gait in individuals with incomplete spinal cord injury. Physiol Rep. 2019 Dec;7(24): e14328.

119. Prosperini L, Pozzilli C. The clinical relevance of force platform measures in multiple sclerosis: a review. Mult Scler Int. 2013; 2013:756564.

120. Takeoka A, Vollenweider I, Courtine G, Arber S. Muscle spindle feedback directs locomotor recovery and circuit reorganization after spinal cord injury. Cell. 2014 Dec 18;159(7):1626–39.

121. Backus D, Cordo P, Gillott A, Kandilakis C, Mori M, Raslan AM. Assisted movement with proprioceptive stimulation reduces impairment and restores function in incomplete spinal cord injury. Arch Phys Med Rehabil. 2014 Aug;95(8):1447–53.

122. Takeoka A. Proprioception: Bottom-up directive for motor recovery after spinal cord injury. Neurosci Res. 2020 May; 154:1–8.

123. Wulf MJ, Tom VJ. Consequences of spinal cord injury on the sympathetic nervous system. Front Cell Neurosci. 2023; 17:999253.

124. Sezer N, Akkuş S, Uğurlu FG. Chronic complications of spinal cord injury. World J Orthop. 2015 Jan 18;6(1):24–33.

125. Curt A, Nitsche B, Rodic B, Schurch B, Dietz V. Assessment of autonomic dysreflexia in patients with spinal cord injury. J Neurol Neurosurg Psychiatry. 1997 May;62(5):473–7.

126. West CR, Popok D, Crawford MA, Krassioukov AV. Characterizing the Temporal Development of Cardiovascular Dysfunction in Response to Spinal Cord Injury. J Neurotrauma. 2015 Jun;32(12):922–30.

127. Grimm DR, Chandy D, Almenoff PL, Schilero G, Lesser M. Airway Hyperreactivity in Subjects With Tetraplegia Is Associated with Reduced Baseline Airway Caliber. CHEST. 2000 Nov 1;118(5):1397–404.

128. Sankari A, Badr MS, Martin JL, Ayas NT, Berlowitz DJ. Impact Of Spinal Cord Injury on Sleep: Current Perspectives. Nat Sci Sleep. 2019; 11:219–29.

129. Liu C, Huang C, Yang Y, Chen S, Weng M, Huang M. Relationship between neurogenic bowel dysfunction and health-related quality of life in persons with spinal cord injury. J Rehabil Med. 2009;41(1):35–40.

130. Stiens SA, Bergman SB, Goetz LL. Neurogenic bowel dysfunction after spinal cord injury: clinical evaluation and rehabilitative management. Arch Phys Med Rehabil. 1997 Mar;78(3 Suppl): S86-102.

131. Han SJ, Kim CM, Lee JE, Lee TH. Colonoscopic lesions in patients with spinal cord injury. J Spinal Cord Med. 2009;32(4):404–7.

132. Schmidt KD, Chan CW. Thermoregulation and fever in normal persons and in those with spinal cord injuries. Mayo Clin Proc. 1992 May;67(5):469–75.

133. Alexander MS, Biering-Sorensen F, Bodner D, Brackett NL, Cardenas D, Charlifue S, et al. international standards to document remaining autonomic function after spinal cord injury. Spinal Cord. 2009 Jan;47(1):36–43.

134. Wecht JM, Krassioukov AV, Alexander M, Handrakis JP, McKenna SL, Kennelly M, et al. International Standards to document Autonomic Function following SCI (ISAFSCI): Second Edition. Top Spinal Cord Inj Rehabil. 2021;27(2):23–49.

135. El-Kotob R, Craven BC, Mathur S, Ditor DS, Oh P, Miyatani M, et al. Assessing Heart Rate Variability as a Surrogate Measure of Cardiac Autonomic Function in Chronic Traumatic Spinal Cord Injury. Top Spinal Cord Inj Rehabil. 2018;24(1):28–36.

136. Illigens BMW, Gibbons CH. Sweat testing to evaluate autonomic function. Clin Auton Res Off J Clin Auton Res Soc. 2009 Apr;19(2):79–87.

137. Taweel WA, Seyam R. Neurogenic bladder in spinal cord injury patients. Res Rep Urol. 2015; 7:85–99.

138. Krogh K, Christensen P, Sabroe S, Laurberg S. Neurogenic bowel dysfunction score. Spinal Cord. 2006 Oct;44(10):625–31.

139. Darrow DP, Balser DY, Freeman D, Pelrine E, Krassioukov A, Phillips A, et al. Effect of epidural spinal cord stimulation after chronic spinal cord injury on volitional movement and cardiovascular function: study protocol for the phase II open label-controlled E-STAND trial. BMJ Open. 2022 Jul 18;12(7): e059126.

140. Walter M, Lee AHX, Kavanagh A, Phillips AA, Krassioukov AV. Epidural Spinal Cord Stimulation Acutely Modulates Lower Urinary Tract and Bowel Function Following Spinal Cord Injury: A Case Report. Front Physiol. 2018; 9:1816.

141. Lance JW. The control of muscle tone, reflexes, and movement: Robert Wartenberg Lecture. Neurology. 1980 Dec;30(12):1303–13.

142. Decq P. [Pathophysiology of spasticity]. Neurochirurgie. 2003 May;49(2-3 Pt 2):163–84.

143. Sköld C, Levi R, Seiger A. Spasticity after traumatic spinal cord injury: nature, severity, and location. Arch Phys Med Rehabil. 1999 Dec;80(12):1548–57.

144. Elbasiouny SM, Moroz D, Bakr MM, Mushahwar VK. Management of spasticity after spinal cord injury: current techniques and future directions. Neurorehabil Neural Repair. 2010 Jan;24(1):23–33.

145. Li Y, Gorassini MA, Bennett DJ. Role of persistent sodium and calcium currents in motoneuron firing and spasticity in chronic spinal rats. J Neurophysiol. 2004 Feb;91(2):767–83.

146. Bennett DJ, Sanelli L, Cooke CL, Harvey PJ, Gorassini MA. Spastic long-lasting reflexes in the awake rat after sacral spinal cord injury. J Neurophysiol. 2004 May;91(5):2247–58.

147. McCOUCH GP, Austin GM, Liu CN, Liu CY. Sprouting as a cause of spasticity. J Neurophysiol. 1958 May;21(3):205–16.

148. Stevenson VL. Rehabilitation in practice: Spasticity management. Clin Rehabil. 2010 Apr;24(4):293–304.

149. Beres-Jones JA, Johnson TD, Harkema SJ. Clonus after human spinal cord injury cannot be attributed solely to recurrent muscle-tendon stretch. Exp Brain Res. 2003 Mar;149(2):222–36.

150. Rekand T, Hagen EM, Grønning M. Spasticity following spinal cord injury. Tidsskr Den Nor Laegeforening Tidsskr Prakt Med Ny Raekke. 2012 Apr 30;132(8):970–3.

151. Biering-Sørensen F, Nielsen JB, Klinge K. Spasticity-assessment: a review. Spinal Cord. 2006 Dec;44(12):708–22.

152. Boyd RN, Graham HK. Objective measurement of clinical findings in the use of botulinum toxin type A for the management of children with cerebral palsy. Eur J Neurol. 1999 Nov;6(S4).

153. Penn RD, Savoy SM, Corcos D, Latash M, Gottlieb G, Parke B, et al. Intrathecal baclofen for severe spinal spasticity. N Engl J Med. 1989 Jun 8;320(23):1517–21.

154. Akman MN, Bengi R, Karatas M, Kilinç S, Sözay S, Ozker R. Assessment of spasticity using isokinetic dynamometry in patients with spinal cord injury. Spinal Cord. 1999 Sep;37(9):638–43.

155. Wartenberg R. Pendulousness of the legs as a diagnostic test. Neurology. 1951;1(1):18–24.

156. Little JW, Halar EM. H-reflex changes following spinal cord injury. Arch Phys Med Rehabil. 1985 Jan;66(1):19–22.

157. Toft E. Mechanical and electromyographic stretch responses in spastic and healthy subjects. Acta Neurol Scand Suppl. 1995; 163:1–24.

158. Giovannelli M, Borriello G, Castri P, Prosperini L, Pozzilli C. Early physiotherapy after injection of botulinum toxin increases the beneficial effects on spasticity in patients with multiple sclerosis. Clin Rehabil. 2007 Apr;21(4):331–7.

159. Coffey JR, Cahill D, Steers W, Park TS, Ordia J, Meythaler J, et al. Intrathecal baclofen for intractable spasticity of spinal origin: results of a long-term multicenter study. J Neurosurg. 1993 Feb;78(2):226–32.

160. Romeni S, Losanno E, Emedoli D, Albano L, Agnesi F, Mandelli C, et al. High-frequency epidural electrical stimulation reduces spasticity and facilitates walking recovery in patients with spinal cord injury. Sci Transl Med. 2025 Jan 8;17(780): eadp9607.

161. Colloca L, Ludman T, Bouhassira D, Baron R, Dickenson AH, Yarnitsky D, et al. Neuropathic pain. Nat Rev Dis Primer. 2017 Feb 16; 3:17002.

162. D'Angelo R, Morreale A, Donadio V, Boriani S, Maraldi N, Plazzi G, et al. Neuropathic pain following spinal cord injury: what we know about mechanisms, assessment and management. Eur Rev Med Pharmacol Sci. 2013 Dec;17(23):3257–61.

163. Nakae A, Nakai K, Yano K, Hosokawa K, Shibata M, Mashimo T. The animal model of spinal cord injury as an experimental pain model. J Biomed Biotechnol. 2011;2011:939023.

164. Costigan M, Scholz J, Woolf CJ. Neuropathic pain: a maladaptive response of the nervous system to damage. Annu Rev Neurosci. 2009; 32:1–32.

165. Hulsebosch CE, Hains BC, Crown ED, Carlton SM. Mechanisms of chronic central neuropathic pain after spinal cord injury. Brain Res Rev. 2009 Apr;60(1):202–13.

166. Baron R, Hans G, Dickenson AH. Peripheral input and its importance for central sensitization. Ann Neurol. 2013 Nov;74(5):630–6.

167. Clark AK, Old EA, Malcangio M. Neuropathic pain and cytokines: current perspectives. J Pain Res. 2013; 6:803–14.

168. Boucher TJ, McMahon SB. Neurotrophic factors and neuropathic pain. Curr Opin Pharmacol. 2001 Feb;1(1):66–72.

169. Martikainen IK, Nuechterlein EB, Peciña M, Love TM, Cummiford CM, Green CR, et al. Chronic Back Pain Is Associated with Alterations in Dopamine Neurotransmission in the Ventral Striatum. J Neurosci Off J Soc Neurosci. 2015 Jul 8;35(27):9957–65.

170. Gustin SM, Peck CC, Cheney LB, Macey PM, Murray GM, Henderson LA. Pain and plasticity: is chronic pain always associated with somatosensory cortex activity and reorganization? J Neurosci Off J Soc Neurosci. 2012 Oct 24;32(43):14874–84.

171. Wrigley PJ, Press SR, Gustin SM, Macefield VG, Gandevia SC, Cousins MJ, et al. Neuropathic pain and primary somatosensory cortex reorganization following spinal cord injury. Pain. 2009 Jan;141(1–2):52–9.

172. Finnerup NB, Baastrup C. Spinal cord injury pain: mechanisms and management. Curr Pain Headache Rep. 2012 Jun;16(3):207–16.

173. Lee S, Zhao X, Hatch M, Chun S, Chang E. Central Neuropathic Pain in Spinal Cord Injury. Crit Rev Phys Rehabil Med. 2013;25(3–4):159–72.

174. Bouhassira D, Attal N, Alchaar H, Boureau F, Brochet B, Bruxelle J, et al. Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4). Pain. 2005 Mar;114(1–2):29–36.

175. Bouhassira D, Attal N, Fermanian J, Alchaar H, Gautron M, Masquelier E, et al. Development and validation of the Neuropathic Pain Symptom Inventory. Pain. 2004 Apr;108(3):248–57.

176. Siddall PJ, Loeser JD. Pain following spinal cord injury. Spinal Cord. 2001 Feb;39(2):63–73.

177. Yalcin I, Choucair-Jaafar N, Benbouzid M, Tessier LH, Muller A, Hein L, et al. beta (2)-adrenoceptors are critical for antidepressant treatment of neuropathic pain. Ann Neurol. 2009 Feb;65(2):218–25.

178. Luo ZD, Chaplan SR, Higuera ES, Sorkin LS, Stauderman KA, Williams ME, et al. Upregulation of dorsal root ganglion (alpha)2(delta) calcium channel subunit and its correlation with allodynia in spinal nerve-injured rats. J Neurosci Off J Soc Neurosci. 2001 Mar 15;21(6):1868–75.

179. De Ridder D, Plazier M, Kamerling N, Menovsky T, Vanneste S. Burst spinal cord stimulation for limb and back pain. World Neurosurg. 2013 Nov;80(5):642-649.e1.

180. Cioni B, Meglio M, Pentimalli L, Visocchi M. Spinal cord stimulation in the treatment of paraplegic pain. J Neurosurg. 1995 Jan;82(1):35–9.

181. Lang P. The treatment of chronic pain by epidural spinal cord stimulation--a 15 year follow up; present status. Axone. 1997 Jun;18(4):71–3.

182. Kumar K, Toth C, Nath RK. Deep brain stimulation for intractable pain: a 15-year experience. Neurosurgery. 1997 Apr;40(4):736–46; discussion 746-747.

183. Courtine G, Song B, Roy RR, Zhong H, Herrmann JE, Ao Y, et al. Recovery of supraspinal control of stepping via indirect propriospinal relay connections after spinal cord injury. Nat Med. 2008 Jan;14(1):69–74.

184. Courtine G, Sofroniew MV. Spinal cord repair: advances in biology and technology. Nat Med. 2019 Jun;25(6):898–908.

185. Ballermann M, Fouad K. Spontaneous locomotor recovery in spinal cord injured rats is accompanied by anatomical plasticity of reticulospinal fibers. Eur J Neurosci. 2006 Apr;23(8):1988–96.

186. Müllner A, Gonzenbach RR, Weinmann O, Schnell L, Liebscher T, Schwab ME. Lamina-specific restoration of serotonergic projections after Nogo-A antibody treatment of spinal cord injury in rats. Eur J Neurosci. 2008 Jan;27(2):326–33.

187. Oudega M, Perez MA. Corticospinal reorganization after spinal cord injury. J Physiol. 2012 Aug 15;590(16):3647–63.

188. Baker SN, Perez MA. Reticulospinal Contributions to Gross Hand Function after Human Spinal Cord Injury. J Neurosci Off J Soc Neurosci. 2017 Oct 4;37(40):9778–84.

189. Fleming JC, Norenberg MD, Ramsay DA, Dekaban GA, Marcillo AE, Saenz AD, et al. The cellular inflammatory response in human spinal cords after injury. Brain J Neurol. 2006 Dec;129(Pt 12):3249–69.

190. Chen K, Yu W, Zheng G, Xu Z, Yang C, Wang Y, et al. Biomaterial-based regenerative therapeutic strategies for spinal cord injury. NPG Asia Mater. 2024 Jan 19;16(1):5.

191. Zheng XQ, Huang JF, Lin JL, Zhu YX, Wang MQ, Guo ML, et al. Controlled release of baricitinib from a thermos-responsive hydrogel system inhibits inflammation by suppressing JAK2/STAT3 pathway in acute spinal cord injury. Colloids Surf B Biointerfaces. 2021 Mar; 199:111532.

192. Xu C, Zhang M, Zhang G, Yan S, Yan W. Hydrogen Sulfide Improves Functional Recovery in Rat Traumatic Spinal Cord Injury Model by Inducing Nuclear Translocation of NF-E2-Related Factor 2. Biol Pharm Bull. 2021 Aug 1;44(8):1093–100.

193. Luo J, Borgens R, Shi R. Polyethylene glycol immediately repairs neuronal membranes and inhibits free radical production after acute spinal cord injury. J Neurochem. 2002 Oct;83(2):471–80.

194. Zhang T, Lin F, Liu W, Liu Y, Guo Z, Xiao C, et al. Reactive oxide species-scavenging lipid-polymer nanoparticles for neuroprotection after spinal cord injury. Appl Mater Today. 2021 Sep; 24:101109.

195. Requejo-Aguilar R, Alastrue-Agudo A, Cases-Villar M, Lopez-Mocholi E, England R, Vicent MJ, et al. Combined polymer-curcumin conjugate and ependymal progenitor/stem cell treatment enhances spinal cord injury functional recovery. Biomaterials. 2017 Jan; 113:18–30.

196. Matsushita T, Lankford KL, Arroyo EJ, Sasaki M, Neyazi M, Radtke C, et al. Diffuse and persistent blood-spinal cord barrier disruption after contusive spinal cord injury rapidly recovers following intravenous infusion of bone marrow mesenchymal stem cells. Exp Neurol. 2015 May; 267:152–64.

197. McKay CA, Pomrenke RD, McLane JS, Schaub NJ, DeSimone EK, Ligon LA, et al. An injectable, calcium responsive composite hydrogel for the treatment of acute spinal cord injury. ACS Appl Mater Interfaces. 2014 Feb 12;6(3):1424–38.

198. Azizi M, Farahmandghavi F, Joghataei MT, Zandi M, Imani M, Bakhtiari M, et al. ChABC-loaded PLGA nanoparticles: A comprehensive study on biocompatibility, functional recovery, and axonal regeneration in animal model of spinal cord injury. Int J Pharm. 2020 Mar 15; 577:119037.

199. Zou Y, Ma D, Shen H, Zhao Y, Xu B, Fan Y, et al. Aligned collagen scaffold combination with human spinal cord-derived neural stem cells to improve spinal cord injury repair. Biomater Sci. 2020 Sep 21;8(18):5145–56.

200. Nazari B, Kazemi M, Kamyab A, Nazari B, Ebrahimi-Barough S, Hadjighassem M, et al. Fibrin hydrogel as a scaffold for differentiation of induced pluripotent stem cells into oligodendrocytes. J Biomed Mater Res B Appl Biomater. 2020 Jan;108(1):192–200.

201. Kushchayev SV, Giers MB, Hom Eng D, Martirosyan NL, Eschbacher JM, Mortazavi MM, et al. Hyaluronic acid scaffold has a neuroprotective effect in hemisection spinal cord injury. J Neurosurg Spine. 2016 Jul;25(1):114–24.

202. Chedly J, Soares S, Montembault A, von Boxberg Y, Veron-Ravaille M, Mouffle C, et al. Physical chitosan microhydrogels as scaffolds for spinal cord injury restoration and axon regeneration. Biomaterials. 2017 Sep; 138:91–107.

203. Sitoci-Ficici KH, Matyash M, Uckermann O, Galli R, Leipnitz E, Later R, et al. Non-functionalized soft alginate hydrogel promotes locomotor recovery after spinal cord injury in a rat hemimyelonectomy model. Acta Neurochir (Wien). 2018 Mar;160(3):449–57.

204. Han S, Lee JY, Heo EY, Kwon IK, Yune TY, Youn I. Implantation of a Matrigel-loaded agarose scaffold promotes functional regeneration of axons after spinal cord injury in rat. Biochem Biophys Res Commun. 2018 Feb 12;496(3):785–91.

205. Yang B, Wang PB, Mu N, Ma K, Wang S, Yang CY, et al. Graphene oxide-composited chitosan scaffold contributes to functional recovery of injured spinal cord in rats. Neural Regen Res. 2021 Sep;16(9):1829–35.

206. McGuire TK, Stasiewicz M, O'Connor C, Woods I, Maughan J, Dobricic M, et al. Development of a PTEN-siRNA activated scaffold to promote axonal regrowth following spinal cord injury. Bioact Mater. 2026 Jun; 60:724–43.

207. Williams RR, Henao M, Pearse DD, Bunge MB. Permissive Schwann cell graft/spinal cord interfaces for axon regeneration. Cell Transplant. 2015;24(1):115–31.

208. Capogrosso M, Wenger N, Raspopovic S, Musienko P, Beauparlant J, Bassi Luciani L, et al. A computational model for epidural electrical stimulation of spinal sensorimotor circuits. J Neurosci Off J Soc Neurosci. 2013 Dec 4;33(49):19326–40.

209. Levine AJ, Hinckley CA, Hilde KL, Driscoll SP, Poon TH, Montgomery JM, et al. Identification of a cellular node for motor control pathways. Nat Neurosci. 2014 Apr;17(4):586–93.

210. Moraud EM, Capogrosso M, Formento E, Wenger N, DiGiovanna J, Courtine G, et al. Mechanisms Underlying the Neuromodulation of Spinal Circuits for Correcting Gait and Balance Deficits after Spinal Cord Injury. Neuron. 2016 Feb 17;89(4):814–28.

211. Formento E, Minassian K, Wagner F, Mignardot JB, Le Goff-Mignardot CG, Rowald A, et al. Electrical spinal cord stimulation must preserve proprioception to enable locomotion in humans with spinal cord injury. Nat Neurosci. 2018 Dec;21(12):1728–41.

212. Wenger N, Moraud EM, Gandar J, Musienko P, Capogrosso M, Baud L, et al. Spatiotemporal neuromodulation therapies engaging muscle synergies improve motor control after spinal cord injury. Nat Med. 2016 Feb;22(2):138–45.

213. Capogrosso M, Milekovic T, Borton D, Wagner F, Moraud EM, Mignardot JB, et al. A brain-spine interface alleviating gait deficits after spinal cord injury in primates. Nature. 2016 Nov 10;539(7628):284–8.

214. Ethier C, Oby ER, Bauman MJ, Miller LE. Restoration of grasp following paralysis through brain-controlled stimulation of muscles. Nature. 2012 May 17;485(7398):368–71.

215. Bouton CE, Shaikhouni A, Annetta NV, Bockbrader MA, Friedenberg DA, Nielson DM, et al. Restoring cortical control of functional movement in a human with quadriplegia. Nature. 2016 May 12;533(7602):247–50.

216. Ajiboye AB, Willett FR, Young DR, Memberg WD, Murphy BA, Miller JP, et al. Restoration of reaching and grasping movements through brain-controlled muscle stimulation in a person with tetraplegia: a proof-of-concept demonstration. Lancet. 2017 May 6;389(10081):1821–30.

217. Zareen N, Shinozaki M, Ryan D, Alexander H, Amer A, Truong DQ, et al. Motor cortex and spinal cord neuromodulation promote corticospinal tract axonal outgrowth and motor recovery after cervical contusion spinal cord injury. Exp Neurol. 2017 Nov; 297:179–89.

218. Tazoe T, Perez MA. Effects of repetitive transcranial magnetic stimulation on recovery of function after spinal cord injury. Arch Phys Med Rehabil. 2015 Apr;96(4 Suppl): S145-155.

219. Wagner FB, Mignardot JB, Le Goff-Mignardot CG, Demesmaeker R, Komi S, Capogrosso M, et al. Targeted neurotechnology restores walking in humans with spinal cord injury. Nature. 2018 Nov 1;563(7729):65–71.

220. Hachmann JT, Yousak A, Wallner JJ, Gad PN, Edgerton VR, Gorgey AS. Epidural spinal cord stimulation as an intervention for motor recovery after motor complete spinal cord injury. J Neurophysiol. 2021 Dec 1;126(6):1843–59.

221. Seáñez I, Capogrosso M. Motor improvements enabled by spinal cord stimulation combined with physical training after spinal cord injury: review of experimental evidence in animals and humans. Bioelectron Med. 2021 Oct 28;7(1):16.

222. Verrills P, Sinclair C, Barnard A. A review of spinal cord stimulation systems for chronic pain. J Pain Res. 2016; 9:481–92.

223. Simopoulos T, Sharma S, Aner M, Gill JS. A Temporary vs. Permanent Anchored Percutaneous Lead Trial of Spinal Cord Stimulation: A Comparison of Patient Outcomes and Adverse Events. Neuromodulation J Int Neuromodulation Soc. 2018 Jul;21(5):508–12.

224. Pahapill PA. Surgical paddle-lead placement for screening trials of spinal cord stimulation. Neuromodulation J Int Neuromodulation Soc. 2014 Jun;17(4):346–8; discussion 348.

225. Caylor J, Reddy R, Yin S, Cui C, Huang M, Huang C, et al. Spinal cord stimulation in chronic pain: evidence and theory for mechanisms of action. Bioelectron Med. 2019 Jun 28; 5:12.

226. Mendell LM. Constructing and deconstructing the gate theory of pain. Pain. 2014 Feb;155(2):210–6.

227. Saadé NE, Tabet MS, Soueidan SA, Bitar M, Atweh SF, Jabbur SJ. Supraspinal modulation of nociception in awake rats by stimulation of the dorsal column nuclei. Brain Res. 1986 Mar 26;369(1–2):307–10.

228. Ji RR, Berta T, Nedergaard M. Glia and pain: is chronic pain a gliopathy? Pain. 2013 Dec;154 Suppl 1(0 1):S10–28.

229. Watkins LR, Milligan ED, Maier SF. Spinal cord glia: new players in pain. Pain. 2001 Sep;93(3):201–5.

230. Yakhnitsa V, Linderoth B, Meyerson BA. Spinal cord stimulation attenuates dorsal horn neuronal hyperexcitability in a rat model of mononeuropathy. Pain. 1999 Feb;79(2–3):223–33.

231. Kapural L, Yu C, Doust MW, Gliner BE, Vallejo R, Sitzman BT, et al. Novel 10-kHz High-frequency Therapy (HF10 Therapy) Is Superior to Traditional Low-frequency Spinal Cord Stimulation for the Treatment of Chronic Back and Leg Pain: The SENZA-RCT Randomized Controlled Trial. Anesthesiology. 2015 Oct;123(4):851–60.

232. Linderoth B, Foreman RD. Conventional and Novel Spinal Stimulation Algorithms: Hypothetical Mechanisms of Action and Comments on Outcomes. Neuromodulation J Int Neuromodulation Soc. 2017 Aug;20(6):525–33.

233. De Ridder D, Vanneste S, Plazier M, van der Loo E, Menovsky T. Burst spinal cord stimulation: toward paresthesia-free pain suppression. Neurosurgery. 2010 May;66(5):986–90.

234. Quindlen-Hotek JC, Kent AR, De Anda P, Kartha S, Benison AM, Winkelstein BA. Changes in Neuronal Activity in the Anterior Cingulate Cortex and Primary Somatosensory Cortex with Nonlinear Burst and Tonic Spinal Cord Stimulation. Neuromodulation J Int Neuromodulation Soc. 2020 Jul;23(5):594–604.

235. Cook AW. Electrical stimulation in multiple sclerosis. Hosp Pract. 1976 Apr;11(4):51–8.

236. Dimitrijevic MR, Gerasimenko Y, Pinter MM. Evidence for a spinal central pattern generator in humans. Ann N Y Acad Sci. 1998 Nov 16; 860:360–76

237. Herman R, He J, D'Luzansky S, Willis W, Dilli S. Spinal cord stimulation facilitates functional walking in a chronic, incomplete spinal cord injured. Spinal Cord. 2002 Feb;40(2):65–8.

238. Harkema SJ, Legg Ditterline B, Wang S, Aslan S, Angeli CA, Ovechkin A, et al. Epidural Spinal Cord Stimulation Training and Sustained Recovery of Cardiovascular Function in Individuals with Chronic Cervical Spinal Cord Injury. JAMA Neurol. 2018 Dec 1;75(12):1569–71.

239. Darrow D, Balser D, Netoff TI, Krassioukov A, Phillips A, Parr A, et al. Epidural Spinal Cord Stimulation Facilitates Immediate Restoration of Dormant Motor and Autonomic Supraspinal Pathways after Chronic Neurologically Complete Spinal Cord Injury. J Neurotrauma. 2019 Aug 1;36(15):2325–36.

240. Davis R, Gray E, Kudzma J. Beneficial augmentation following dorsal column stimulation in some neurological diseases. Appl Neurophysiol. 1981;44(1–3):37–49.

241. Waltz JM. Spinal cord stimulation: a quarter century of development and investigation. A review of its development and effectiveness in 1,336 cases. Stereotact Funct Neurosurg. 1997;69(1-4 Pt 2):288–99.

242. Jones ML, Evans N, Tefertiller C, Backus D, Sweatman M, Tansey K, et al. Activity-based therapy for recovery of walking in chronic spinal cord injury: results from a secondary analysis to determine responsiveness to therapy. Arch Phys Med Rehabil. 2014 Dec;95(12):2247–52.

243. Quel de Oliveira C, Refshauge K, Middleton J, de Jong L, Davis GM. Effects of Activity-Based Therapy Interventions on Mobility, Independence, and Quality of Life for People with Spinal Cord Injuries: A Systematic Review and Meta-Analysis. J Neurotrauma. 2017 May 1;34(9):1726–43.

244. Rowald A, Komi S, Demesmaeker R, Baaklini E, Hernandez-Charpak SD, Paoles E, et al. Activity-dependent spinal cord neuromodulation rapidly restores trunk and leg motor functions after complete paralysis. Nat Med. 2022 Feb;28(2):260–71.

245. Kathe C, Skinnider MA, Hutson TH, Regazzi N, Gautier M, Demesmaeker R, et al. The neurons that restore walking after paralysis. Nature. 2022 Nov;611(7936):540–7.

246. Courtine G, Gerasimenko Y, van den Brand R, Yew A, Musienko P, Zhong H, et al. Transformation of nonfunctional spinal circuits into functional states after the loss of brain input. Nat Neurosci. 2009 Oct;12(10):1333–42.

247. Lorach H, Galvez A, Spagnolo V, Martel F, Karakas S, Intering N, et al. Walking naturally after spinal cord injury using a brain-spine interface. Nature. 2023 Jun;618(7963):126–33.

248. North RB, Sung JH, Matthews LA, Zander HJ, Lempka SF. Postural Changes in Spinal Cord Stimulation Thresholds: Current and Voltage Sources. Neuromodulation J Int Neuromodulation Soc. 2024 Jan;27(1):178–82.

249. Reddy CG, Dalm BD, Flouty OE, Gillies GT, Howard MA, Brennan TJ. Comparison of Conventional and Kilohertz Frequency Epidural Stimulation in Patients Undergoing Trialing for Spinal Cord Stimulation: Clinical Considerations. World Neurosurg. 2016 Apr; 88:586–91.

250. Nugent SM, Lovejoy TI, Shull S, Dobscha SK, Morasco BJ. Associations of Pain Numeric Rating Scale Scores Collected during Usual Care with Research Administered Patient Reported Pain Outcomes. Pain Med. 2021 Oct 8;22(10):2235–41.

251. Darnall BD, Sturgeon JA, Cook KF, Taub CJ, Roy A, Burns JW, et al. Development and Validation of a Daily Pain Catastrophizing Scale. J Pain. 2017 Sep;18(9):1139–49.

252. Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care. 1992 Jun;30(6):473–83.

253. Patel YA, Butera RJ. Challenges associated with nerve conduction block using kilohertz electrical stimulation. J Neural Eng. 2018 Jun;15(3):031002.

254. Pelot NA, Behrend CE, Grill WM. Modeling the response of small, myelinated axons in a compound nerve to kilohertz frequency signals. J Neural Eng. 2017 Aug;14(4):046022.

255. Gill ML, Grahn PJ, Calvert JS, Linde MB, Lavrov IA, Strommen JA, et al. Neuromodulation of lumbosacral spinal networks enables independent stepping after complete paraplegia. Nat Med. 2018 Nov;24(11):1677–82.

256. Danner SM, Hofstoetter US, Freundl B, Binder H, Mayr W, Rattay F, et al. Human spinal locomotor control is based on flexibly organized burst generators. Brain J Neurol. 2015 Mar;138(Pt 3):577–88.

257. Jung Y, Breitbart S, Malvea A, Bhatia A, Ibrahim GM, Gorodetsky C. Epidural Spinal Cord Stimulation for Spasticity: a Systematic Review of the Literature. World Neurosurg. 2024 Mar; 183:227-238.e5.