ABSTRACT

A Complete Review of Spinal Cord Injury with a Focus in Engineering Techniques in Spinal Cord Injury Research

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Spinal cord injury (SCI) is a crippling neurological disorder that yields physical, behavioral, social, and financial consequences. Globally, thousands of people suffer from SCI-inducing accidents every year. Despite SCI being studied for nearly 1700 years, research progress has led largely to palliative instead of curative care. Over the previous few decades, however, researchers have made remarkable progress in understanding the pathophysiology of SCI, therefore informing what clinical interventions may be made to alleviate the consequences of SCI. Current interventions involve intravenous methylprednisolone, surgical treatments to re-align and decompress the spine, and rehabilitation. Current experimental treatments have shown promise in delivering lower risk solutions, especially with a recent surge of computational and engineering techniques in medicine. This review offers a thorough and up-to-date account of SCI research and modern, as well as potential, clinical treatments. This review begins with an overview of spinal cord anatomy, clinical definitions, SCI pathophysiology, and modern clinical options for SCI and potential risks associated. Lastly, this review covers engineering therapeutic advancements that may further shift current clinical options for SCI to the curative side of care.

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A COMPLETE REVIEW OF SPINAL CORD INJURY WITH A FOCUS IN ENGINEERING TECHNIQUES IN SPINAL CORD INJURY RESEARCH

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CHAPTER ONE

Introduction

The Edwin Smith Papyrus, an ancient Egyptian papyrus dating roughly back to 1700 BC, reported Spinal cord injury (SCI) as an "ailment not to be treated" (van Middendorp et al., 2010). Even today, nearly 40 centuries later, the treatments for SCI are far from curative, and instead largely center on how to remediate symptoms associated with SCI such as: reducing spasticity and pain syndromes; averting injury advancement; and educating those suffering from SCI on how to manage the psychological and social consequences of SCI disabilities (Silva et al., 2014). Fortunately, however, advancements in technology and neurobiological research, both concerning and not concerning SCI, have enabled researchers to shift the treatment of SCI from being largely palliative to, hopefully, curative.

Today, there are approximately 250,000 SCI victims, and 12,000 new cases every year in the United States (NINDS, 2020). World-wide, roughly 2.5 million people suffer from SCI, with more than 130,000 new incidents being reported annually (Thuret et al., 2006). Causes include penetrating bullet wounds (26%), non-penetrating wounds from accidents involving vehicles (38%), accidents related to sports (7%), and, particularly in the elderly, falls (22%). Furthermore, an estimated 50% of SCI victims suffer from complete sensorimotor impairment below the lesion (Dobkin, 2003). In addition to a lack of locomotive control beneath the lesion, SCI victims may also suffer from bacterial and viral infections in the bladder and kidneys, bowel issues, increased risk of diabetes, and

respiratory complications, emphasizing the totality of the consequences that SCI victims experience. Unfortunately, more than 95% of patients are unable to regain the ability to walk (Dobkin, 2003). Additionally, patients must abide by constant financial obligations. For example, one-year post-injury and -rehab, patients with complete paraplegia owe, on average, $20,000 in medical expenses annually. This figure increased to approximately $95,000 annually for those with complete tetraplegia (NSCISC, 1998). Given the medical, social, and financial prevalence of this problem, it is imperative to develop approaches that may solve this issue.

This review will supply an in-depth synopsis of the SCI field, pulled from academic sources, discussing anatomical and pathophysiological information concerning SCI, it's research progress and clinical applications, and the future of SCI research with a particular emphasis in engineering devices to solve this problem.

CHAPTER TWO

Anatomy of the Spinal Cord

The description below pertains only to the human spinal cord, unless otherwise noted. Spinal cords from other animals, such as rats, differ from that of humans. This is an important distinction to make especially when considering animals as a model to study SCI.

The spinal cord itself is a long, tubular structure composed of nervous tissue connecting the brain to the peripheral nerves branching from the cord. The cord is roughly 40 to 50 cm in length, and 1 to 1.5 cm in diameter in a fully developed human. Its main function is to provide a means of communication between the central (CNS) and the peripheral (PNS) nervous system. The spinal cord is divided into four different regions: cervical (C), thoracic (T), lumbar (L), and sacral (S). The cervical region of the cord is located from the neck to the upper back, the thoracic cord, the middle back, the lumbar, lower back, and sacrum, the tailbone region (Fig. 2.0). It extends from the foramen magnum, where it also merges with the medulla, to only the first or second lumbar vertebrae in humans, or the third lumbar vertebrae in the case of rats. This is because the vertebral column grows at a faster rate than the spinal cord, and thus the cord does not pass through the entire vertebral column (Silva et al., 2014).

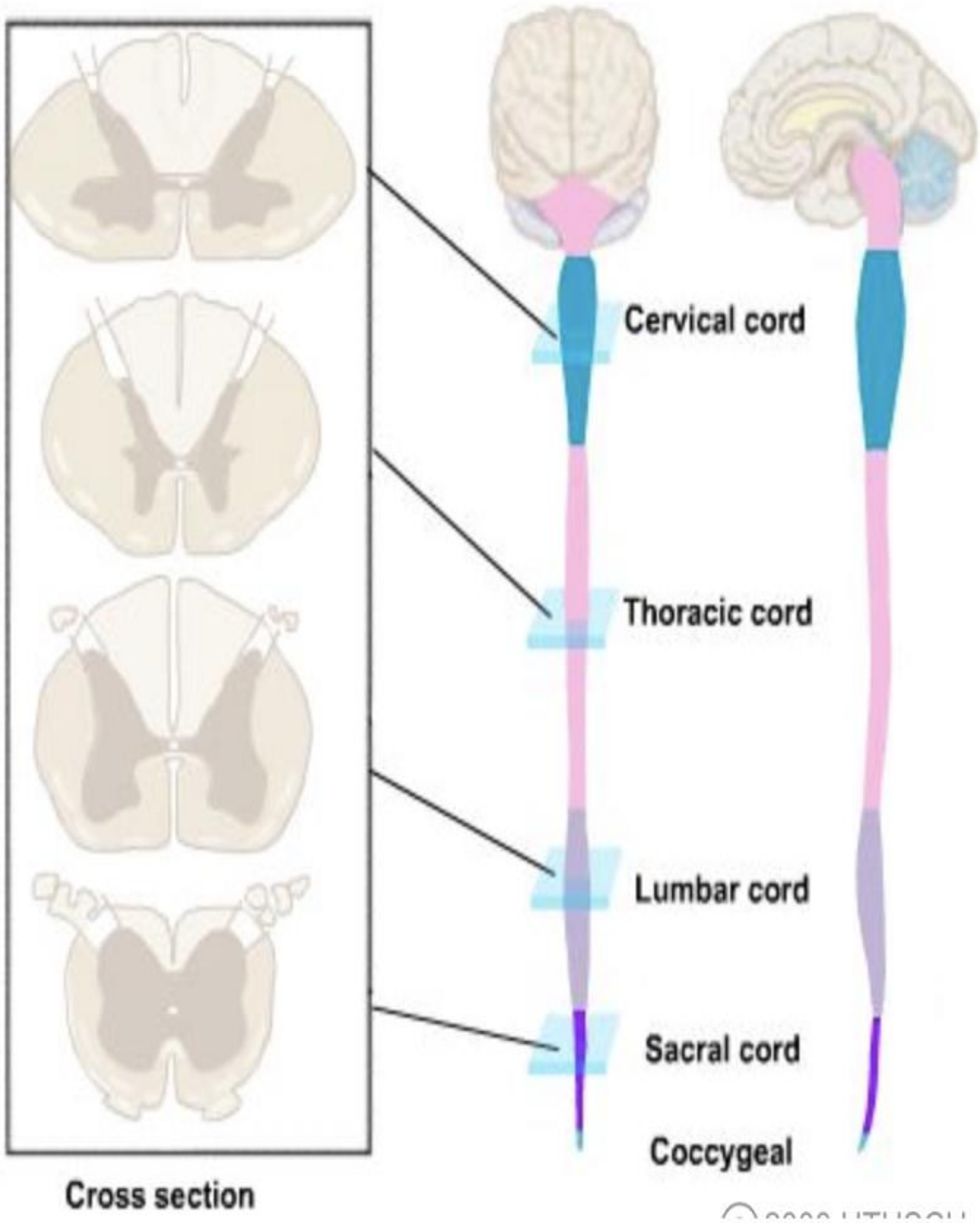

Fig 2.0. Schematic dorsal and lateral view of the four cross sections of the cervical, thoracic, lumbar, and sacral cord. (Source adapted from Dafny, 2000)

The spinal cord is protected by 33 rings of bone, dubbed vertebrae, and between each vertebra, nervous tissue extends from the spinal cord to the body. There are 31 different spinal nerves extending from the cord: 8 of the 31 are C nerves which are responsible for controlling the muscles and glands of, and receiving sensory input from, the neck, shoulders, arms, and hands; 12 T nerves conduct a similar function as the C nerves, except for the chest and abdominal region; 5 L nerves analogous with the hip and leg regions; 5 S nerves analogous with the genital and lower digestive region; and 1 coccygeal nerve which relate only to the skin region over the coccyx (Fig. 2.1) (Silva et al., 2014).

In addition to the vertebrae, other anatomical guards are put in place to protect the cord. Three membranes, which are named from the inner- to the outermost layer, wrap around the cord serving as further protection of the CNS: the pia mater, arachnoid, and dura mater (Purves, 2004). Furthermore, the cerebrospinal fluid (CSF), found in the center of the cord, mitigates SCI through acting as a shock-absorber, where it reduces the force impacted on the cord.

The nervous tissue making up the spinal cord is split into two different types: white and gray matter. The ratio of gray to white matter increases significantly from the cervical region down to the sacral region, in part because the tracts found in the white matter are less necessary further down the cord. At the very center of the cord, a tiny canal, called the central canal, carries CSF to nourish the surrounding nervous tissue (Dafny, 2000).

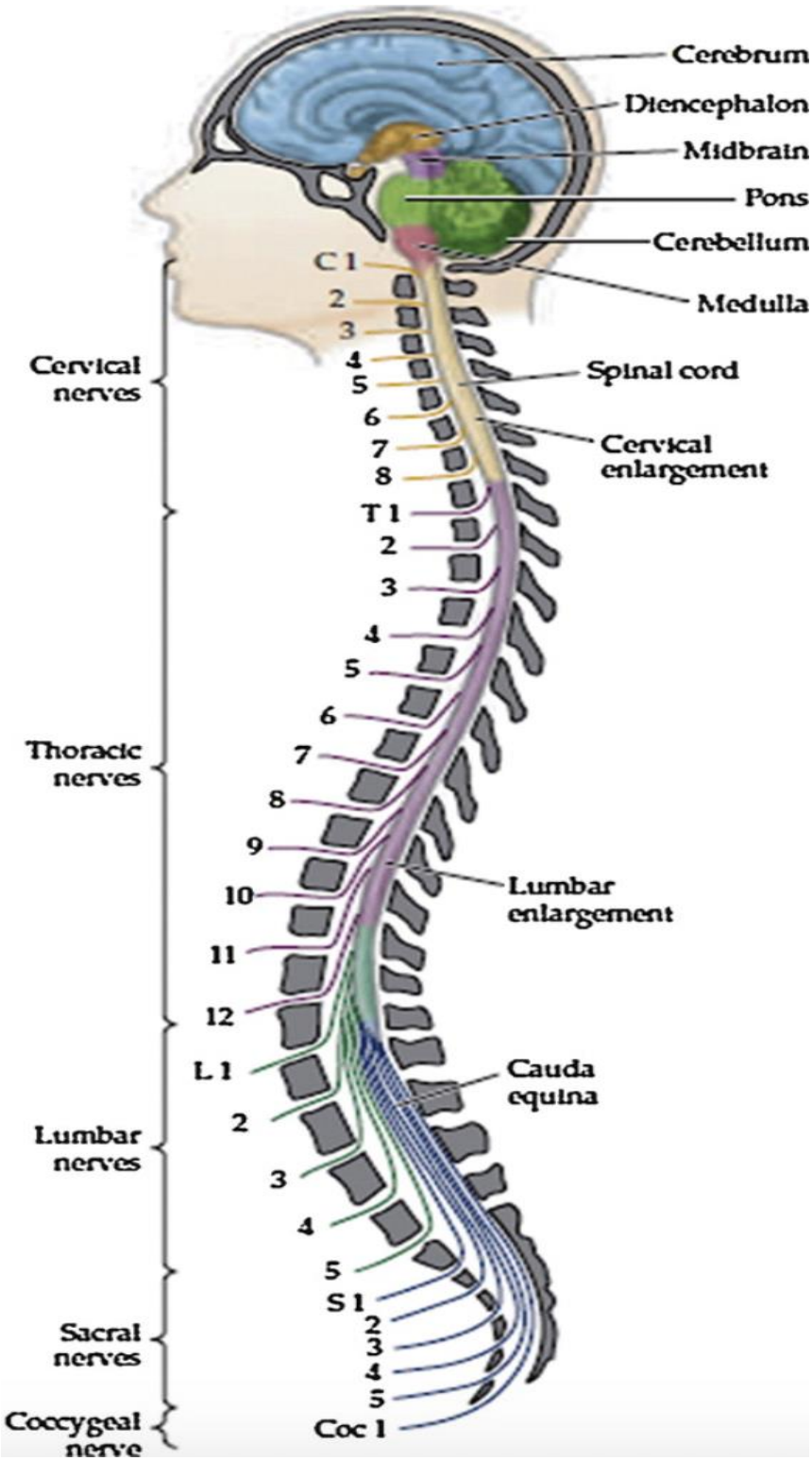

Fig 2.1. Representation of all 31 spinal nerves in the human spinal cord (Source adapted from Purves et al., 2004).

White matter is found in the peripheral of the cord. White matter mostly consists of myelinated nerve fibers, and is therefore called “white” matter, since myelin often exhibits a white-ish color. These myelinated nerve fibers run longitudinally throughout the cord and consist of both ascending and descending tracts to either relay information to the brain, or transmit information from the brain, respectively (Fig. 2.2). Tracts are groups of nerve fibers that share the origin and destination of the fibers, and, oftentimes, functions of each particular fiber. White matter is organized into 3 different columns: the dorsal (or posterior) column, the ventral (or anterior) column, and the lateral columns. Ascending tracts (the tracts which transmit sensory information to the brain from sensory receptors) are found in all 3 columns. Descending tracts (the tracts which transmit information associated with motor activity from the brain to various areas throughout the body) are found only in the anterior and lateral columns (Dafny, 2000).

The nerve fibers which make up the ascending tract all originate from the first order neuron located in the dorsal root ganglia, which, as the name suggests, is found on the dorsal side of the spine (Fig. 2.3). A first order neuron is the first neuron in a chain or tract of neurons. In order for the first order neuron to initiate information transmission, a stimulus must first initiate an action potential in the first order neuron to then cause a transmission of information throughout the chain of neurons. Moreover, if the first neuron in a chain of neurons is called the first order neuron, then, in the same mode of thinking, the second neuron in the chain would be called the second order neuron, and so on. All the ascending tracts in the white matter carry sensory information to the brain. Thus, a stimulus from say one’s finger would then travel through sensory neurons to the dorsal root of the spinal nerve, and then synapse with the secondary neuron to then bring

the information to the brain. For example, the ascending gracile and cuneate fasciculi, often called the dorsal funiculus (funiculus being a bundle of neural fibers surrounded by connective tissue), resides in the dorsal column of the white matter, and carries information pertaining to tactility, proprioception, and vibration, from the world external to the brain (Dafny, 2000) (Fig. 2.2).

Conversely, the first order neurons in the descending tracts are found in different cortical areas and brain stem nuclei. These tracts are responsible for disseminating information associated with motor ability, like posture, balance, muscle tone, and reflex activity (Dafny, 2000). Opposed to the afferent (ascending) tracts, these efferent (descending) tracts travel down the spinal cord, exit the spinal cord on the ventral side via the ventral roots, and then deliver the message originated in the brain to the targeted muscle or tissue via motor neurons. The lateral corticospinal tract, for example, begins in the cerebral cortex and decussates throughout the medulla down the lateral column to control voluntary, fine movements of the limbs ipsilateral to the tract (Fig. 2.2) (Saladin, 2012).

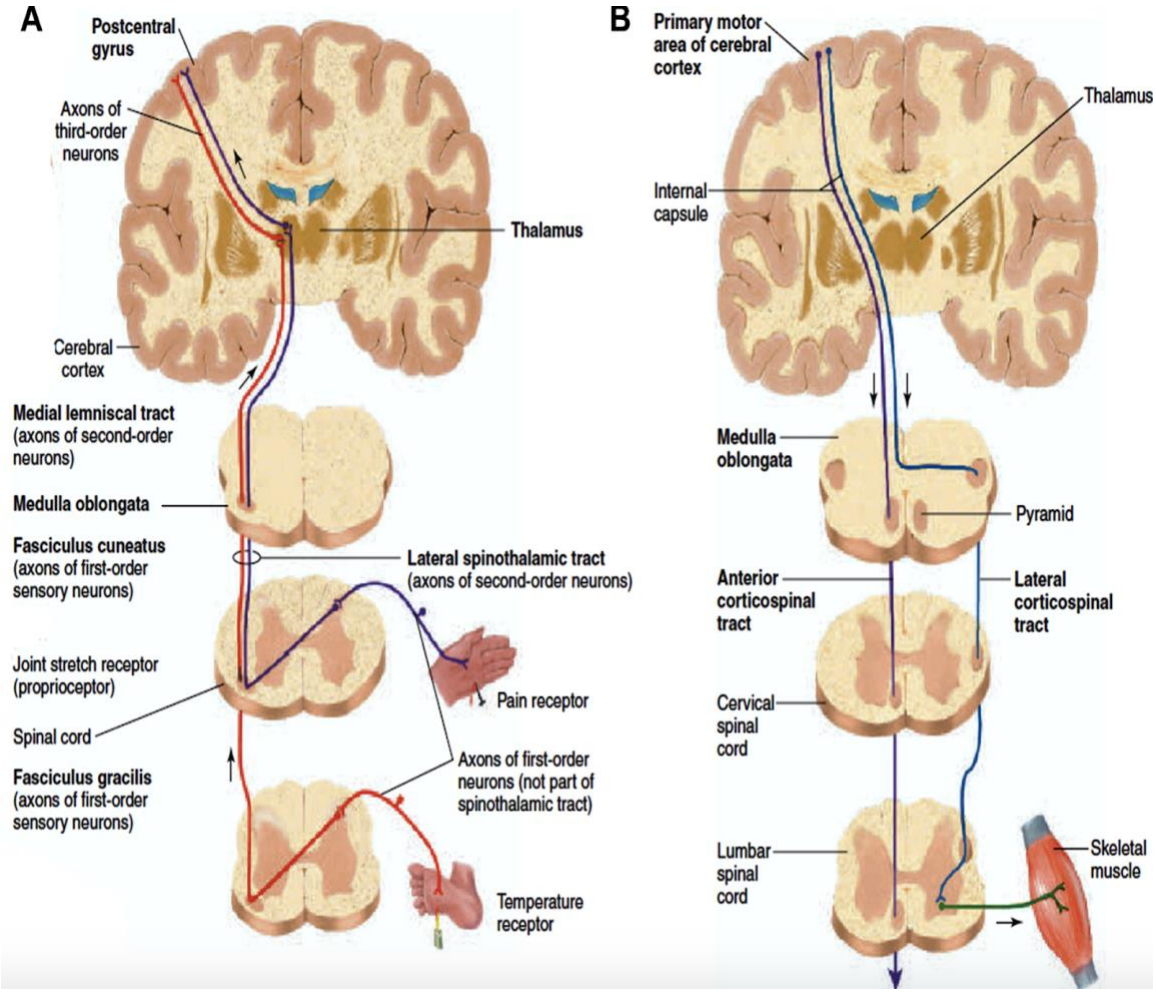

Fig 2.2. "Example of ascending and descending spinal tracts. (A) Lateral spinothalamic tract carrying sensorial information (pain and temperature impulses) from the periphery to the brain. (B) Descending corticospinal motor tracts. These motor tracts contain axons that pass from the precentral gyrus of the cerebral cortex down the spinal cord to make synapses with spinal interneurons and lower motor neurons." (Source and description adapted from Vander, et al., 2001)

The gray matter is found in the cord's central areas, shaped like the letter "H" (Fig. 2.0, 2.3), and contributes to spinal cord function through conducting the actual synapsis of the neurons. Gray matter consists of motor neuron cell bodies and their dendrites, glia and axon terminals. Gray matter is termed "gray" since its contents (cell bodies, dendrites, synapses etc.) are an off-white color due to the contents' lack of

myelin. The gray matter is segmented into four main columns: the dorsal, ventral, and lateral horn columns, and the intermediate column (Fig. 2.4).

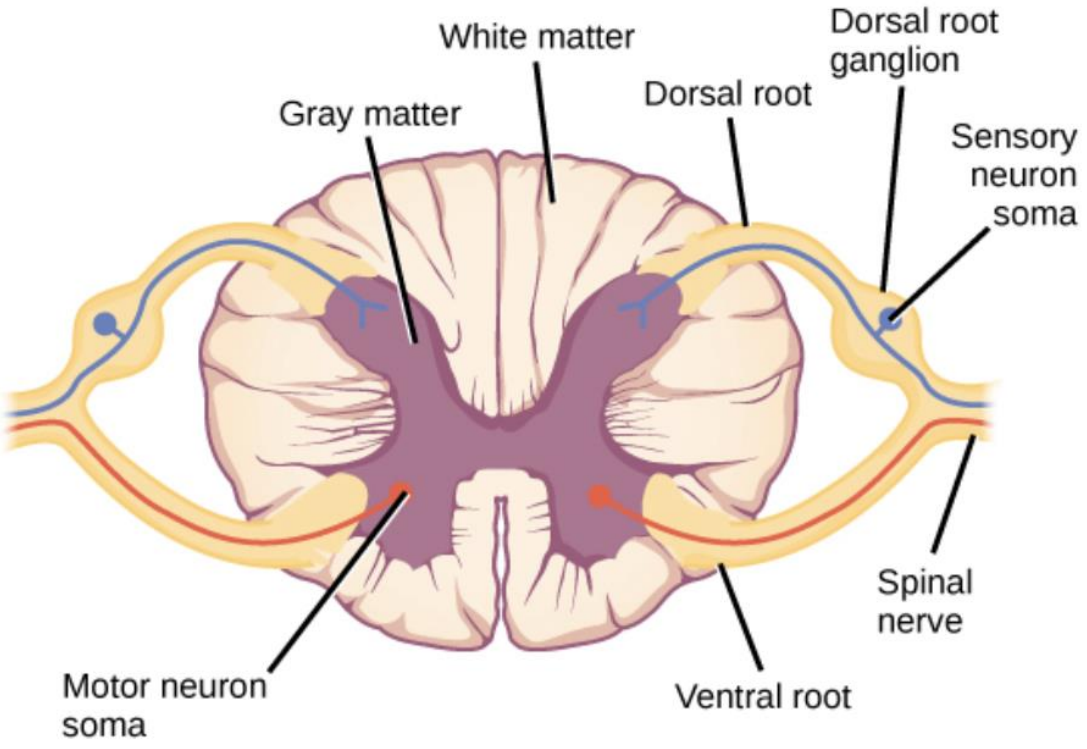

Fig 2.3. Cross section of spinal cord detailing locations of the white matter, gray matter, dorsal and ventral roots, and the sensory and motor neuron somas. (Source adapted from UNSW Sydney Embryology, 2018)

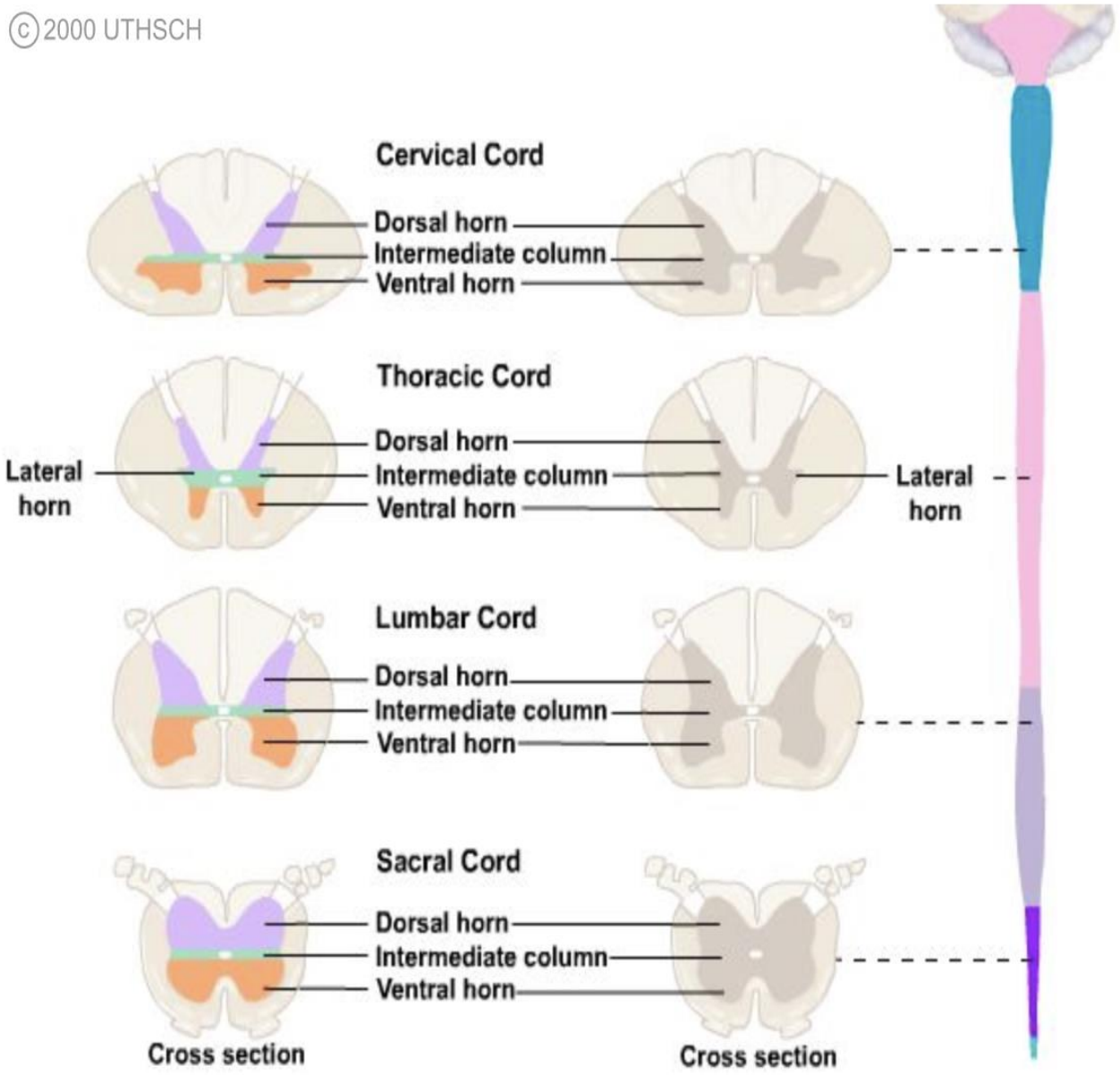

Fig 2.4. Organization of the dorsal, ventral, and lateral horn columns, and the intermediate column found in the spinal cord's gray matter. (Source adapted from Dafny, 2000)

The dorsal horn consists of sensory neurons which receive all somatosensory information from the exterior of the brain. Neuronal projections from the dorsal horn then ascend into the midbrain region and the diencephalon where they transmit the sensory

information originally received. The intermediate and lateral horn columns consist of autonomic neurons and are responsible for controlling pelvic and visceral organs. The ventral horn consists of motor neurons responsible for skeletomuscular control (Dafny, 2000).

CHAPTER THREE

Clinical Descriptions of Spinal Cord Injury Cases

Within the clinic, physicians and other medical professionals use the following terms to describe different aspects of SCI patients (Kirshblum et al., 2011):

Tetraplegia: This term refers to a SCI that occurred in the spinal cord within the cervical region, or above the first thoracic vertebrae, that resulted in a loss motor or sensory function. Depending on the level of injury, tetraplegics lose motor or sensory function in all four limbs, the trunk, and the pelvic organs.

Paraplegia: This term refers to a SCI that occurred in the spinal cord within the thoracic, lumbar, or sacral region, or below the last cervical vertebrae, that resulted in a loss motor or sensory function. Depending on the level of injury, paraplegics lose motor or sensory function in the trunk, legs, or pelvic organs.

Dermatome: This term refers to the skin area that is supplied by sensory nerves from each respective spinal root (Fig. 3.0).

Myotome: This term refers to the group of muscles that is supplied by the motor nerves from each respective spinal root. It is important to note that muscles share motor nerves segments, and therefore assigning a particular muscle to a certain spinal root is a simplification (Fig. 3.1). If a muscle is controlled by more than one different segment, than a weakening of the respective myotome may be due to the absence of innervation from one of the multiple segments.

Sensory level: The sensory level is determined via a physician performing an examination of the 28 key sensory points (dermatomes) on left and right side of the body

(Fig. 3.0). Physicians measure sensation through three different mediums: i) light pressure through softly stroking the dermatome, ii) heavy pressure through firmly pressing on the dermatome, and iii) sharp sensation through a pin prick. The most caudal dermatome is deemed the sensory level.

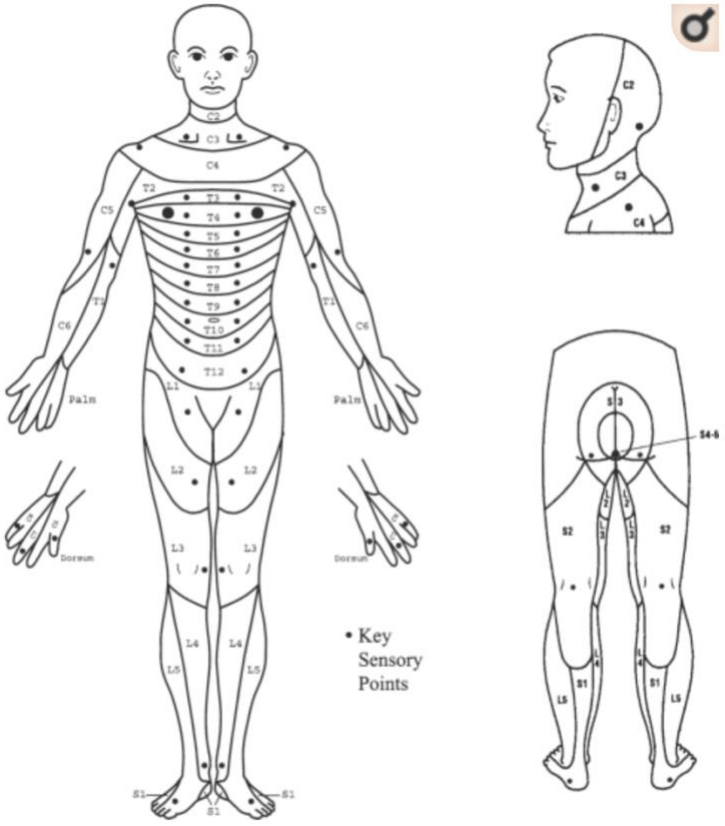

Fig 3.0. Diagram depicting the 28 key sensory points within each of the 28 dermatomes that physicians use to determine the overall sensory level of an SCI patient. (Source adapted from Kirshblum et al., 2011)

Motor level: The motor level is determined via examining the muscle function within the 10 different myotomes on the right and left side of the body (Fig. 3.1) according to the Manual Muscle Testing (MMT) from the NIH. The motor level is the lowest muscle that has a grade of at least 3 (Table 3.0).

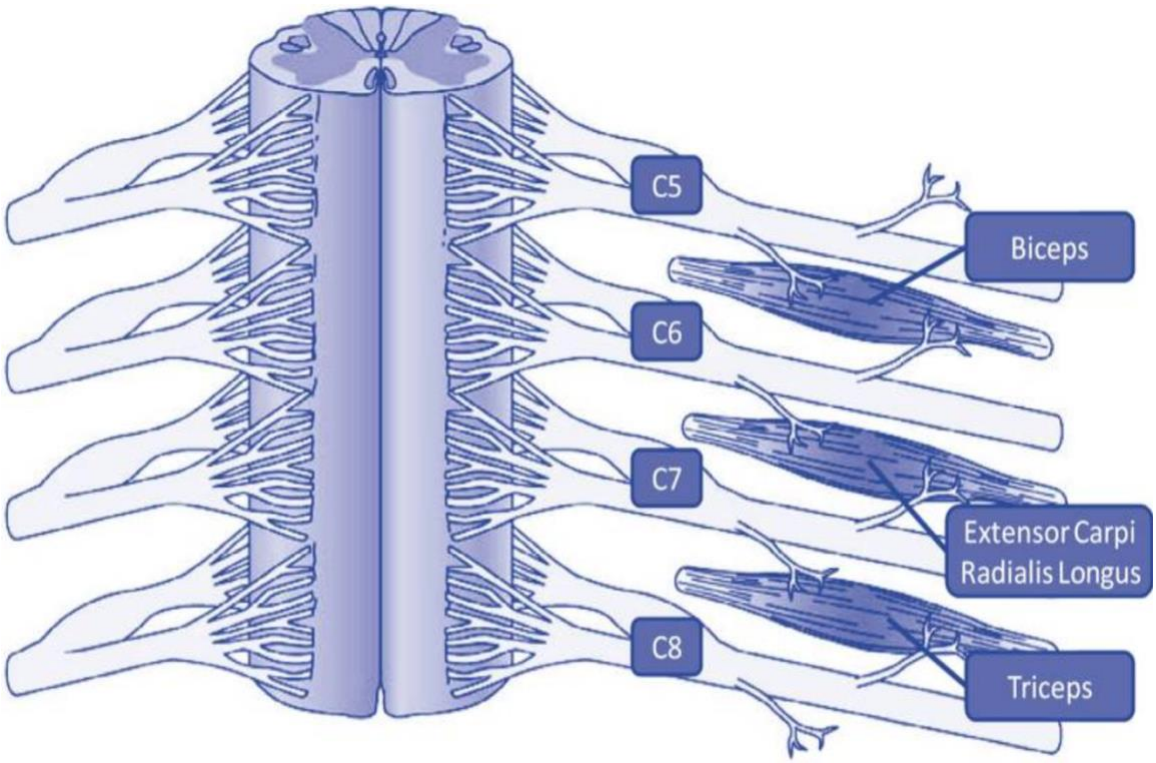

Fig. 3.1. Schematic demonstrating 3 different myotomes, namely the Biceps, extensor carpi radialis longus, and triceps. Each myotome is controlled by two different nerve segments. The bicep is controlled by the C5 and C6 nerves, the extensor carpi radialis longus, the C6 and C7 nerves, and the triceps, the C7 and C8 nerves. (Source adapted from Kirshblum et al., 2011)

Table 3.0. Descriptions on how to grade motor level in SCI patients. (Source adapted from niehs.nih.gov).

MANUAL MUSCLE TESTING PROCEDURES

Key to Muscle Grading

	Function of the Muscle	Grade		
No Movement	No contractions felt in the muscle	0	0	Zero
	Tendon becomes prominent or feeble contraction felt in the muscle, but no visible movement of the part	T	1	Trace
Test Movement	**MOVEMENT IN HORIZONTAL PLANE**			
	Moves through partial range of motion	1	2-	Poor-
	Moves through complete range of motion	2	2	Poor
	ANTIGRAVITY POSITION	3	2+	
	Moves through partial range of motion			
Test Position	*Gradual* release from test position	4	3-	Fair-
	Holds test position (no added pressure)	5	3	Fair
	Holds test position against slight pressure	6	3+	Fair+
	Holds test position against slight to moderate pressure	7	4-	Good-
	Holds test position against moderate pressure	8	4	Good
	Holds test position against moderate to strong pressure	9	4+	Good+
	Holds test position against strong pressure	10	5	Normal

Neurological level of injury (NLI): The NLI measures the sensory and antigravity motor function of the most caudal region of the spinal cord. These measurements often differ in the left and right side of the cord, as well as in their sensory and motor function, therefore giving rise to four segments to be examined for the NLI: Right-motor, Left-motor, Right-sensory, and Left-sensory.

Incomplete injury: This term is used when the SCI patient has retained some sensory or motor function below the spinal cord lesion. Those diagnosed with incomplete injury also include those who have sensation in the sacral region. This can be measured through deep anal pressure (DAP), where the examiner inserts a finger and applying pressure to the anorectal wall. A patient who can feel this sensation is said to have "sacral sparing".

Complete injury: This term is used when the SCI patient has no sensation or motor control in the lowest sacral segments. Thus, DAP would yield no sensation to a patient who has experienced "complete injury", and this patient would be said to not have "sacral sparing".

Zone of partial preservation (ZPP): This term is only used with complete injury patients and refers to the myotomes and dermatomes that are the most caudal, but still are capable of motor and sensory function.

Physicians use the American Spinal Injury Association (ASIA) impairment scale (AIS) to determine the grade of SCI (American Spinal Injury Association, 2000). The following scale is used to measure the degree of dysfunction in SCI patients:

A (Complete): The SCI patient has no motor or sensory function in the sacral vertebrae, S4-S5. In other words, DAP would result in no motor or sensory function.

B (Sensory Incomplete): The SCI patient maintains sensory capabilities, but not motor function, below the spinal cord lesion, and must include sensation of the sacral region. Furthermore, motor function is not preserved more than three levels below the motor level on both the left and right side of the body.

C (Motor Incomplete): The SCI patient maintains motor function below the lesion, and at least more than half of key muscle functions below the NLI have an MMT grade that is

less than 3. Furthermore, the patient ought to be able to voluntarily contract the anal sphincter.

D (Motor Incomplete): The SCI patient maintains motor function below the lesion, and at least more than half of key muscle functions below the NLI have an MMT grade that is more than 3. Furthermore, the patient ought to be able to voluntarily contract the anal sphincter.

E (Normal): If motor and sensation function are all deemed normal by the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) in all nerve segments (Fig. 3.2). The patient must have had a prior deficit resulting from SCI to receive the “E” grade. Otherwise healthy people do not receive the grade.

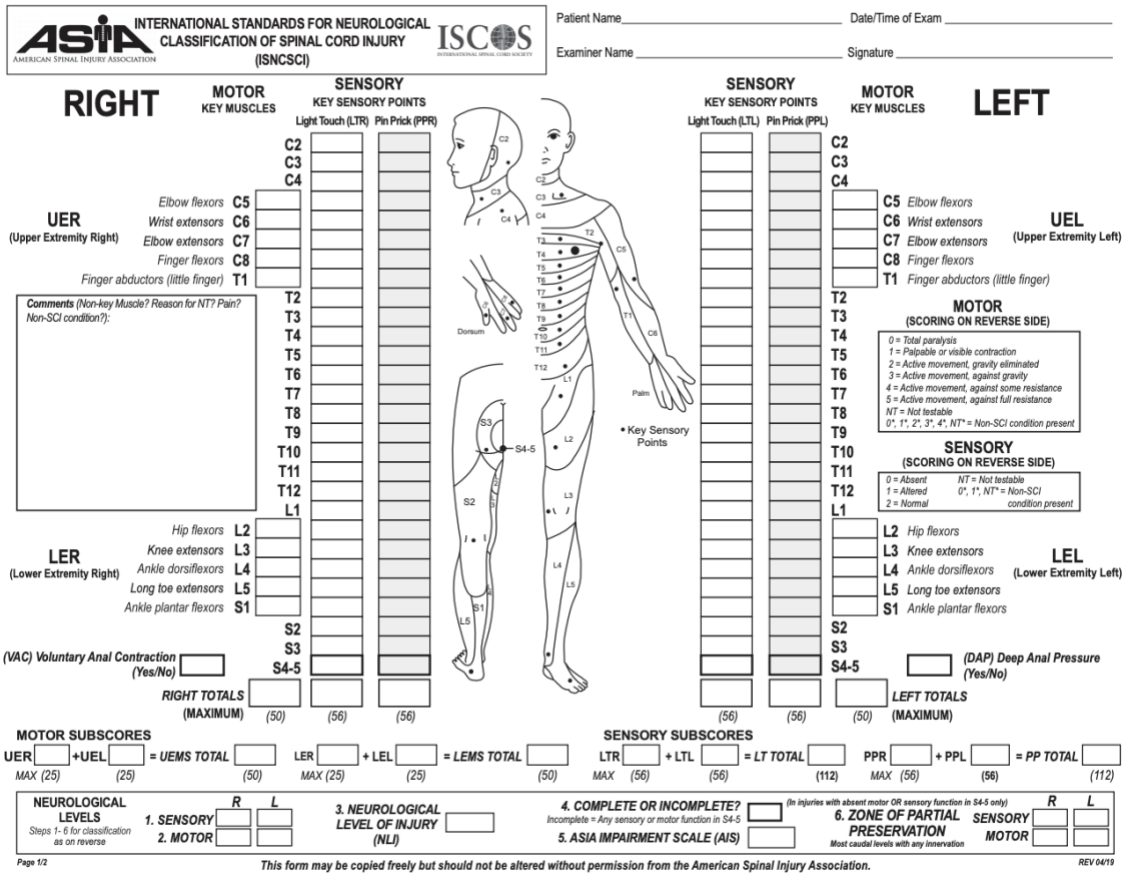

Fig. 3.2. Example of ISNCSCI sheet used to determine the AIS grade to diagnose SCI patients.

CHAPTER FOUR

Pathophysiology of Spinal Cord Injury

Spinal cord lesions, as mentioned in the introduction, oftentimes result from blunt force such as vehicular accidents, sports, bullet wounds, and other sources. However, SCI may also arise from other neurological disorders. For instance, 86% of patients with multiple sclerosis exhibit spinal cord lesions postmortem (Filippi et al., 2014), or cancerous tumors may develop in brain tissue and travel down the CSF, or develop in the spinal cord itself (NINDS, 2019). Furthermore, and much less common, spinal cord tissue infarction via vascular ischemia, and subsequent cell death result in SCI (Munyon and Hart, 2015). Though there are several causes for SCI, the causes related to blunt force resulting in the SCI is referred to as "primary injury" by physicians (USC Spine Center, 2020).

Primary injuries immediately lead to hemorrhaging and cell death at the site of impact and can be binned into four morphologies: impact plus persistent compression, impact alone with transient compression, distraction, and laceration (Oyinbo, 2011). Impact plus persistent compression, the most common primary injury, occurs when bone fragments compress and damage the cord. Impact alone with transient compression occurs most commonly in hyperextension injuries. Distraction injuries, which are fairly uncommon, occur when the cord is stretched, thus causing the column to tear. Lastly, laceration injuries occur when some projectile tears the cord directly, such as a bone fragment or a bullet tearing the cord (Alizadeh et al., 2019).

As a result of primary injury, other consequential, biological events occur over time that compromise the outcome of the victim, dubbed “secondary injury” (USC Spine Center, 2020). Secondary injury processes, in summary, are a cascade of vascular and biochemical events, ultimately leading to a restriction in blood flow, and thus neuronal dysfunction and death. These injuries exacerbate the consequences of SCI, and, when compared with primary injury, are more easily recoverable due to their predictability. Primary injuries often occur without immediate medical personnel nearby, and it is not until a few to several hours until a SCI victim is seen by a medical expert, where secondary injuries have already begun. Thus, most research efforts have been made towards mitigating the secondary injury mechanisms, and reducing cell loss following primary injury (Oyinbo, 2011).

Since secondary injuries are so often targeted for the treatment of SCI patients, it is important to have an in-depth understanding of them. The biological response (secondary injury) to the primary injury is temporally divided into three phases which are not strict in their allotted time interval: acute (seconds to minutes following the injury), sub-acute (minutes to weeks following the injury), and chronic (months to years following the injury) (Table 4.0).

Table 4.0. Prominent features of secondary injury seconds to minutes following (acute), hours to weeks following (sub-acute), and months to years following primary injury (chronic). (Source adapted from Oyinbo, 2011)

Major features of the three phases of spinal cord injury		
ACUTE	**SUB-ACUTE**	**CHRONIC**
Systemic hypotension and spinal shock		
Vasospasm	Vasospasm	
Cell death from direct insult	Cell death from direct insult	
Ischemia	Ischemia	
Oedema	Oedema	
Derangements in ionic homeostasis	Derangements in ionic homeostasis	
Accumulation of neurotransmitters	Glutamatergic excitotoxicity	
Plasma membrane compromise	Plasma membrane compromise / permeability	
	Free-radical production	
	Lipid peroxidation	
	Nitrous oxide excess	
	Conduction block	
	Excess noradrenaline	
	Energy failure and decreased ATP	
	Immune cells invasion and release of cytokines	
	Inflammatory mediated cell death	
	Neurite growth-inhibitory factors	
	Central chromatolysis	
	Vertebral compression / column instability	
	Demyelination of surviving axons	Continued demyelination
	Apoptosis	Continued apoptosis
	Initiation of central cavitation	Continued central cavitation
	Astroglial scar launch	Glial scar / syrinx formation
		Alteration of ion channels and receptors
		Regenerative processes, including sprouting by neurons
		Altered neurocircuits
		Syringomyelia

Upper rectangular shade: events common to acute and secondary phase
Lower rectangular shade: events common secondary phase and chronic phase

Several of these biological responses can occur and progress throughout the three phases. Ultimately, these responses are summarized as: changes in the vascular system, formation of free radicals and lipid peroxidation, cell death, inflammatory response, and imbalance in pertinent neuronal ionic species. Minimizing these secondary effects is of the utmost importance, since it could prevent the extension of the lesion and contribute to spinal cord function regeneration.

Vascular changes following blunt trauma compounds the damage on the spinal cord. Systemic effects of acute spinal cord injury, that is seconds to minutes following the primary injury, include decreased cardiac output and subsequent hypotension. At a local level, there is a lack of autoregulation at the injured portion of the spinal cord, and a large decrease in the microcirculation in both the white and gray matter, especially in areas concentrated with hemorrhaging. Blood circulation throughout the cord also decreases as time following the primary injury increases. Furthermore, this loss in the vascular microcirculation can extend to areas beyond just the injury site (Tator and Fehlings, 1991). Due to the hemorrhaging, major histological consequences arise such as the blood brain barrier breaking down, the consequent invasion of inflammatory cells, and infarction of the spinal cord at the injury site.

Free radical formation following primary injury also compromise the health of the patient. Immediately following acute spinal cord injury, free radicals, such as O_2 and H_2O_2, form and a simultaneous depletion of the endogenous antioxidant, glutathione (GSH), which is important for reducing cellular damage from reactive oxygen species (ROS) (hence it being an antioxidant), such as those the free radicals named above. The combination of increased ROS and decreased GSH concentration result in an increase in

oxidative stress markers, ultimately resulting in long term tissue damage (Visavadiya et al., 2016). Furthermore, high ROS concentrations lead to chains of lipid peroxidation reactions significantly contributing to cellular oxidative stress (Jia et al., 2011). This makes the spinal cord especially susceptible to oxidative stress due to its abundance in polyunsaturated fatty acids. Given that ROS-induced lipid peroxidation is a major biological event contributing to the secondary effects of SCI, free radical formation has been a major focus in therapeutic interventions to mitigate SCI consequences (Hall et al., 1992).

Following primary injury cell death may begin in the acute phase and can persist throughout the chronic phase (Table 4.1). There are two prominent types of cell death that occurs following primary injury: necrosis and apoptosis. Due to the consequent vascular changes following blunt force, cells in the spinal cord will lack blood supply--and these cells, and therefore the tissues which the cells make up, will undergo necrosis resulting in a loss of function for that particular tissue (Balentine, 1978). Necrosis, however, occurs during the acute and sub-acute phase only since cells will undergo necrosis upon severe blunt trauma or if ischemia occurs. In addition to necrosis, apoptosis, or programmed cell death, may occur in several cell types within the spinal cord, namely neurons, oligodendrocytes, and glia. Several studies have demonstrated that apoptotic mechanisms persist for several weeks following the primary injury (Keane et al., 1992; Crowe et al., 1997; Beattie et al., 2007). Cells other than neurons undergoing apoptosis may cause severe damage overtime. Apoptosis of oligodendrocytes, for example, is seen weeks following the SCI incident, and contributes to the lack of myelination in the spinal cord following injury (Crowe et al., 1997).

The secondary neuroinflammatory response is mediated through several types of cells, particularly microglia, astrocytes, and infiltrating immune cells (Haussman, 2003). Within the 48- to 72-hour period following injury, leukocytes may flood the injured region and release ROS and pro-inflammatory cytokines, and, therefore, contribute to the lipid peroxidation that occurs following SCI (Mabon et al., 2000). These cells are predominantly found in the gray matter, which is sensible since the gray matter contains the cell bodies (Carlson et al., 1998). This increase in leukocytes and inflammation may also increase extravasation of more leukocytes into the CNS propagating secondary inflammatory damage (Mabon et al., 2000). Inflammation, however, has also been shown to aid in repairing the neural tissue. To do this, though is a challenge. Researchers must track the several types of cells involved in the inflammatory response, their levels overtime, and the nature of their actions at that specific stage (Fleming et al., 2006). Studies in infectious disease and tumor biology have demonstrated that macrophages can be polarized to either a "classically" activated M1 cell that is pro-inflammatory and cytotoxic, or an alternatively activated M2 cell that is anti-inflammatory and therefore reduce ROS and lipid peroxide production (Kigerl et al., 2009).

An imbalance in ionic species such as K^+, Ca^{2+}, and Na^+ further promote secondary injury. White matter heavily depends upon a supply of energy acquired through oxidative phosphorylation. However, since these cells are likely undergoing ischemia, or even anoxia, energy may be severely reduced due to a lack of oxygen and nutrients. Furthermore, ischemia and anoxia may lead to failure of the Na+/K+ ATP-ase, which will lead to an accumulation of axoplasmic Na+ coupled with a deficit of K+ leading to membrane depolarization. This increase in axoplasmic Na+ will promote

axonal Ca2+ overload through the Na+ channels which then activates phospholipases and protein kinase c, and result in tissue damage (Stys, 1998).

CHAPTER FIVE

Current Clinical Interventions for Spinal Cord Injury Patients

Currently, there are no curative treatments for SCI patients. Majority of SCI victims do not regain full motor or sensory function. However, for the current standard of care for SCI patients. Health care providers first work towards stabilizing the spinal cord, followed by decompression of the cord paired with a high dose of methylprednisolone (MP) (Rath and Balain, 2017).

Research on animal models have suggested that decompressing the spinal cord leads to functional recovery and mitigates secondary injury (Dimar et al., 1999). However, other researchers have purported that these findings are not translatable to human studies, and advise against surgical interventions, since patients are not likely to gain significant improvement from decompression, and, instead, increase risk for malpractice during surgery (Rath and Balain, 2017). Some physicians today, however, still choose to decompress the spinal cord based on the currently available evidence. Furthermore, there is evidence that surgical interventions within 24 hours of the injury could decrease the time spent in the intensive care unit and the post-injury medical complications (Fehlings and Perrin 2006). Currently, however, there are no standards regarding the timing and role of decompression in SCI—and may be a possible area for clinicians and researchers to further investigate.

Regarding therapeutic interventions, there are an abundance regeneration-stimulating, neuroprotective agents in clinical trials that may improve neurologic recovery following SCI (Karsy and Hawryluk, 2017). However, currently, the most prescribed, and highly controversial, therapeutic option is MP.

MP is a glucocorticoid, which is a class of corticosteroid that is effective at reducing inflammation and suppressing the immune system. The agent is delivered as a bolus intravenous infusion of 30 mg per kg of body weight over 15 minutes within eight hours of primary injury. MP, specifically, is capable of multiple functions to protect the spinal cord from further secondary damage. MP inhibits lipid peroxidation by acting as a free radical scavenger, reduce inflammation, improve spinal cord blood flow, and assist in maintaining the blood-spinal cord barrier (Tator, 1998). However, other studies have refuted MP as a dependable pharmacologic agent to treat SCI (Hugenholtz et al., 2002). A study involving 330 SCI patients demonstrated no significant difference in motor or sensory neurologic recovery in groups either at 6 or after 6 weeks (Bracken, 1984).

However, Bracken and his group did affirm that a high dose MP treatment results in significant neurological recovery if treated within 8 hours of the primary injury incident (Bracken et al., 1990). These results from Bracken's team only highlights the complexity, and importance of noticing the timing, of SCI treatments. Still, however, some studies suggest that there is insufficient evidence to support the use of MP within 8 hours or past 23 hours following the time of primary injury (Hugenholtz et al., 2002).

It is also important to note the severe side effects that may occur alongside MP treatments. Several studies purporting neurological recovery following a high dose of MP

have also reported an increase in cases of pneumonia, wound infections, pulmonary embolism, gastrointestinal hemorrhages, and, even death (Silva et al., 2014).

Given this controversy, the practice of administering MP has seen a large decrease. Hurlbert and Hamilton claimed that, over a five-year period, MP the percent of patients prescribed MP has decreased from 76% to 24% (Hurlbert and Hamilton, 2008). This decrease was accompanied by an increase in physician exposure to peer-reviewed literature and research conferences—emphasizing the importance of evidence-based medicine when providing proper treatment for patients.

Aside from MP, other pharmacologic agents have been evaluated for SCI treatment (Karsy and Hawryluk, 2017). Ganglioside GM-1, also known as Sygen, is a complex glycolipid found in the nervous tissue membrane. Sygen may promote neurological repair and recovery of motor and sensory function; however, findings are questionable at best. In 1995, a clinical trial in Maryland demonstrated that Sygen treatment resulted in improved grades according to the ASIA motor score as opposed to a placebo treatment in 37 patients (Globus et al., 1995). However, other clinical studies have increased their patient size with over 750 patients and found that patients classified with a Complete ASIA Grade A injury saw less benefit than those with incomplete injuries (Karsy and Hawryluk, 2017).

Other, less studied agents have had potential in mitigating secondary injury effects. Thyrotropin releasing hormone (TRH), for instance, serves as an antagonist for excitotoxic amino acids, peptide-leukotrienes, endogenous opioids, and platelet activating factor in rats. A clinical trial was conducted using TRH and resulted in a significant improvement in motor and sensory function (Pitts et al., 1995). The patient cohort,

however, only consisted of 20 SCI patients, and should therefore be treated with caution. This is the only human clinical trial to test TRH on SCI patients.

This severe lack in therapeutic treatments for neurologic recovery highlights the need for further therapeutic studies. Furthermore, some drugs, such as TRH, have not been as heavily scrutinized, as opposed to MP, thereby demonstrating the lack of current, dependent clinical trials for therapeutic interventions.

CHAPTER SIX

Modern Bioengineering Approaches to Spinal Cord Injury

As mentioned in Chapter Four, the pathophysiology of SCI can be quite complex, involving several different variables that may contribute to the overall outcome for the patient. Therefore, there is a wide variety of approaches scientists have taken today in an attempt to mitigate SCI consequences varying from cell-based therapies like neural stem cell transplantation, to computer engineering approaches, such as developing computer-interfaces for motor control in lieu of the spinal cord. The techniques below have only been applied to animal models.

Some researchers have focused on simply replacing the lost neural tissue using neural stem cells. Neural stem cells (NSC) are multipotent cells capable of differentiating into neurons, astrocytes, or oligodendrocytes that may have been lost due to the SCI. NSCs are abundant since they are found in both the developing and fully-developed CNS, and can be isolated and cultured in vitro for eventual transplantation into the lesion of the spinal cord. Furthermore, NSCs are capable of releasing several neurotrophic factors that would aid in the development of NSCs for the replacement of lost neural tissue (Lu et al., 2003). When NSCs were attempted to be transplanted into the injured spinal cord of a rat model, however, the NSCs did not differentiate into neurons or glial cells. Instead, the NSCs either differentiated into Glial cells or did not differentiate at all (Cao et al., 2001). This led researchers to induce differentiation into a neuronal lineage in vitro before transplantation into the spinal cord. This approach promoted NSC survival rate,

migration, differentiation into neural cells, and an improvement in motor function following transplantation in animals (Lepore and Fischer, 2005).

Though NSCs are promising, there is still a large gap in knowledge regarding the mechanisms by which the transplanted NSCs restore function and ethical problems about the use of fetal NSCs—which may be a leading reason on why NSCs are not so heavily focused on in clinical trials (Silva et al., 2014).

Similar to NSCs, post-natal tissues, like bone marrow or adipose tissue, offers mesenchymal stem cells (MSC) that are accessible and easily differentiable due to their multipotency. Furthermore, they are easier to isolate and culture as opposed to NSCs and have low immunogenic and anti-inflammatory properties (Silva et al., 2014). The most popular MSC source is bone marrow and have been shown to have the ability to differentiate into neurons and glial cells in mice similar to NSCs (Brazelton et al., 2000). The exact mechanism for how bone marrow MSC may contribute to neurologic repair is currently unknown, but the release of neurotrophic factors when the MSCs have been transplanted into the spinal cord has been confirmed (Ribeiro et al., 2011).

Another prominent cell-based therapy for SCI patients is using Schwann Cells (SC) to promote regeneration of nerve axon through various growth factors. SCs are responsible for producing the myelin sheaths that are wrapped around the axons in the PNS. Furthermore, if PNS axons are injured, SCs assist in the regeneration of such axons through secreting multiple growth factors and produce extracellular matrix molecules, like laminin and collagen, that support axon growth (Chernousov and Carey, 2000). SCs, though may not directly replace lost neural tissue, when transplanted will not only support axonal growth in the PNS system but can mitigate loss of myelination in the

spinal cord. For example, Hill and their team demonstrated that implanting SCs near the site of injury caused extensive infiltration of endogenous SCs to the actual site, therefore increasing myelination in that respective area (Hill et al., 2006). Interestingly, though, cells other than SCs accomplished the same effect in the spinal cord. Skin-derived precursors, when implanted, generated myelinating SCs to the injury site and led to an increase in functional recovery in mice with contusion spinal cord injury (Biernaski, et al., 2007). This ultimately suggests that endogenous SCs, not necessarily the transplantation of exogenous SCs, may promote remyelination of the spinal cord and improve sensory and motor function.

There are limitations to SC therapy, however. Corticospinal tracts demonstrate poor regenerative properties and axons are unable to enter or exit neural tissue grafts following SC integration (Keyvan-Fouladi et al., 2005).

Aside from cell-based therapies, researchers are using more quantitatively heavy approaches to mitigating the consequences for SCI. Brain-machine interfaces (BMI) first emerged in 1999 when Chapin and his team first demonstrated an ensemble of cortical neurons that could directly control a robotic manipulator (Chapin et al., 1999). Today, brain-machine interfaces are largely defined by a cortical recording modality, such an electroencephalogram (EEG), that is attached to the motor cortex of the brain, and is capable of relaying the neural output from the brain towards controlling a machine, such as a robotic arms and legs, keyboard keys, and a cursor on a computer (Fig 6.0).

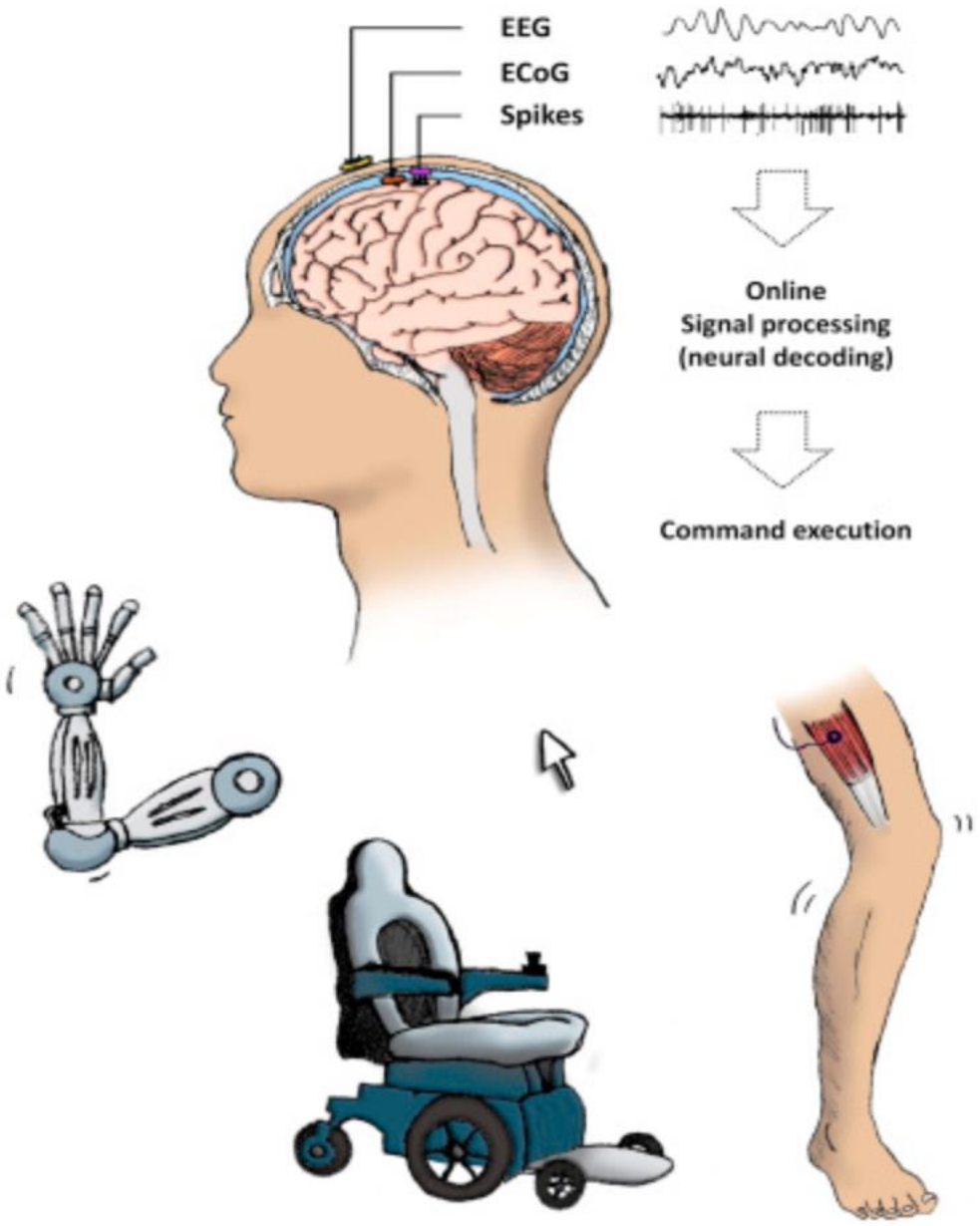

Fig. 6.0. Schematic showing different cortical recording modalities (varying from an EEG, Electrocorticogram (ECoG), and Spikes. EEGs are a non-invasive modality and can record neural activity from the scalp. ECoG penetrates a deeper, and records neural activity from the brain either epi- or subdurally. Single or multi-unit (spikes) recordings penetrate the brain the deepest and can measure neural signals in close proximity to the device. These modalities are used to relay neural information to execute tasks, like powering a wheelchair, controlling a robotic arm, or even electrically simulating certain muscles. (Source adapted from Monzural et al., 2016)

BMIs still have significant limitations that prevent them from being utilized for SCI treatment. The neural interfaces that are inserted into the brain may not be biologically friendly for the brain. Materialistically, current interfaces exhibit low toughness, and break easily, and low adhesion when laminated onto a tissue surface. Furthermore, these interfaces often do little to mitigate inflammation upon insertion into the brain in animal models (Huang et al., 2018). Additionally, the interfaces are not perfect in reading the neural output from the motor cortex. Motor control requires proprioception, such as an SCI patient's estimation of their limb position, which can confound the neural output from the motor cortex and therefore confound the execution of the BMI (Staviskey et al., 2018).

CHAPTER SEVEN

Final Remarks

To date, there is still a lot of progress that remains to be done in an effort to shift SCI treatment from largely palliative to curative care. However, thanks to the progress in understanding the pathophysiology of SCI, the current treatments for those suffering from SCI and the respective benefits and drawbacks, researchers have made large strides in mitigating the consequences that tetraplegics and paraplegics must endure. There exist several cell-based therapies, such as NSC and MSC transplantation to replace lost neural tissue, and SC-based therapy to remyelinate the axons in the spinal cord, that could be further investigated as possible sources of treatments for SCI. Additionally, despite the flaws in the computation, researchers have engineered neural interfaces capable of replacing the motor function of the spinal cord, so that SCI patients who are unable to move limbs can control their own wheelchair or use a computer. Overcoming the shortcomings of cell-based and computer-based discoveries, such as this, remains to be the challenge for researchers to further push for curative care for SCI patients.

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