INERVENTIONS

THE INERVENTION´S METHOD

A review of available therapies against spasticity and the Electro therapy as an alternative

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Index

Abstract

The Upper Motor Neurone Syndrome (UMNS) is defined as alterations in the physiological motor control in the skeletal muscle after an insult and/or lesion in the Central Nervous System (CNS). One of the main components and outcomes is spasticity, known collectively as a “positive” phenomenon characterize by muscle overactivity. Hyperactive spinal reflexes mediate most of these positive phenomena as lesions lead to disturbances of the balance of supraspinal inhibitory and excitatory inputs, producing a state of net disinhibition of the spinal reflexes. When spasticity produces a clinical disability interfering with daily activities, medical treatment is recommended. Currently there are available many different approaches including pharmacological, physical, surgical and electro therapies that will eventually increase the functionality and quality of life of affected individuals by decreasing the level of spasticity as a result of injuries in the CNS at supraspinal (Telencephalon, Cerebellum, Mid Brain) and spinal levels. Knowledge of the electrophysiology and neurochemistry of the spinal reflexes, together with the action of antispasticity drugs and treatments will help us to improve the quality of life of those affected by this syndrome.

Aim and Purpose

Many currently available therapies against spasticity rely on pharmacological effects at the spinal and/or neuromuscular junction level. Their action is narrowed to the inhibition and/or blockade of the synaptic impulses between sensory neurons, inhibitory/excitatory interneurons and Moto neurons. The aim of this document is to point out electro-therapy as a valid option in the treatment of spasticity. More importantly, as we will see through the entire document, the facilitation of neural circuits in the spinal cord from patients with UMNS could help in the neuroplasticity processes that undergo in the nervous system upon an insult or lesion. We do not claim that electric stimulation should replace other therapies or that is the most suitable for any kind of spasticity regardless of the level and impairment that could induce. But as we will show here it can be used as an effective additional therapy that could help to improve the daily management of patients with spasticity. Of course, no treatment is 100% effective and as in many publications, reviews and editorials regarding the study of the medical management of the spasticity, we agree that the combination of electro-therapy with any other form of therapy could improve impairment movements and quality life among patients.

Introduction

The motor system compromises a large number of different cell types (neurons, astrocytes, Schwan cells, macroglia,….), nuclei, synapses and a tight relationship between the central and the peripheral nervous systems (CNS and PNS). The process of movement has in the past been considered a sequence of steps like: Idea→Plan→Select→Move. Nowadays this concept it is not as simplistic, as between the Plan and Select steps there are a broad spectrum of different areas in the CNS participating in order to attain the well-known movement finesse accomplish in all our movements. Nevertheless this "step" approach underestimates the degree to which these elements are performed in parallel. This parallelism ensures a robust system as any damage structure can be compensated, to a certain extent, by activity of other structures. Examples of this compensation can be seen in stroke patients who have undergone physical and non-invasive therapy, improving and recovering their motor skills as a reorganization of their CNS lead by neural plasticity[1-3]. In this introduction we will give a quick and simplified overview of the motor system and its functionality, in order to show later on how the different therapies affect and what are the advantages and disadvantages regarding to their action mechanism.

Neurophysiology of the movement

Much of the brain and nervous system is devoted to the processing of sensory input, in order to construct detailed representations of the external environment. This elaborate processing would be of limited value, however, unless we had a way to act upon the environment that we are sensing, whether that action consist of running away from a predator or seeking shelter against the rain. In some cases the relationship between the sensory input and the motor output are simple and direct, however, our conscious actions require not only sensory input but a host of other cognitive processes that allow us to choose the most appropriate motor output for the given circumstances. In each case, the final output is a set of commands to certain muscles in the body to exert force against some other object or forces (e.g., gravity). This entire process falls under the subject of motor control. The way the motor system accomplish this task relies in two basic principles: Functional segregation (different areas controlling different aspect of movement) and Hierarchical Organization (higher areas take decisions whereas lower areas tune the movements). The motor system hierarchy consists in 4 levels: the spinal cord, the brain stem, the motor cortex and the association cortex, having the cerebellum and the basal ganglia as interconnectors between levels. The highest level compromises the primary motor area (Brodmann´s area 4), the supplementary motor area (Brodmann´s area 6) and regions of the cingulate cortex[4], being the primary motor areas the ones projecting mainly towards the brain stem and the spinal cord through the corticospinal tract and has the densest terminations among the distal muscles of the arms and legs but also innervates all sections of the spinal cord[5]. The activity started in these high level areas represents our voluntary movements. These movements also have the input from subcortical areas helping to coordinate, automatize and adapt these movements. The cerebellum and basal ganglia have no direct motor outputs, however their outputs travel to centres into the thalamus and cortex[6]. Nevertheless sophisticated neural processing is carried at the lowest level of the motor hierarchy, the spinal cord. These processing gives rise to the reflex movements although these automatic movements can be regulated by higher levels of hierarchy which act in parallel to compensate (at least partially) for injuries to other parts of the system.

Descending motor pathways arise from multiple regions of the brain and send axons down the spinal cord and are organized in two major groups:

- Lateral pathways: Controlling both proximal and distal muscles and are responsible for most voluntary movements. They include:
  i. Lateral corticospinal tract[7]: Originated in the motor cortex and its main projection run through the internal capsule (relay station in the descent tract, and one of the main areas where motor and neurodegenerative diseases occur such as Parkinson, Huntington, Cerebral Palsy and stroke). It is the primary pathway that carries the motor commands underlying voluntary movement.

  ii. Rubrospinal tract[7]: Originates in the red nucleus of the midbrain. It is an alternative by which voluntary motor commands can be sent to the spinal cord. It receives inputs from the motor cortex and therefore it is important pathway for the recovery of some voluntary motor functions after damage to the corticospinal tract.
- Medial pathways: Controlling axial muscles and are responsible for posture, balance and coarse of the axial and proximal muscles.
  i. Vestibulospinal tract (both lateral and medial): Originates in the vestibular nuclei (medial and Lateral) it mediates postural adjustments and head movements, moreover it also helps to maintain body balance.

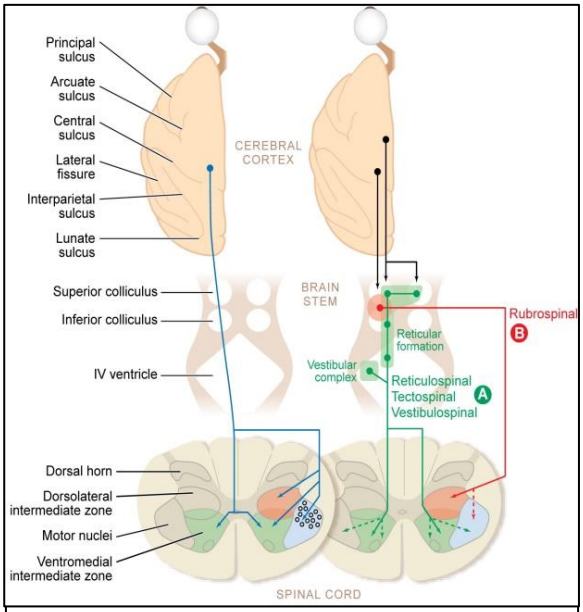


Figure 1. Schematic representations of the distributions of the the Lateral and Medial pathways. On the right, Group A fibers (reticulospinal, tectospinal, vestibulospinal) are shown in green, arising from the brainstem reticular formation, superior colliculus, and vestibular complex. Group B fibers (rubrospinal) are shown in red, arising from the red nucleus. These brainstem pathways receive significant cortical projections (black). On the left, corticospinal projections are shown in blue: Some parallel the group A fibers and terminate bilaterally in the ventromedial IZ (green area), whereas the majority parallel the group B system and terminate contralaterally in the dorsolateral IZ (red area) and directly on motoneurons innervating the arm and hand (blue region with small black circles). *Adapted from Lemon, 2008*

  ii. Reticulspinal tract[8]: Originated in the brainstem, it also represents a major alternative to the corticospinal tract, responsible of the flexor responses and some complex actions such orienting, stretching and posture.
  iii. Tectospinal tract[9,10]: originates in the deep layers of the superior colliculus and crosses the midline immediately. It mediates reflex postural movements of the head in response to visual and auditory stimuli.
  iv. Anterior corticospinal tract.

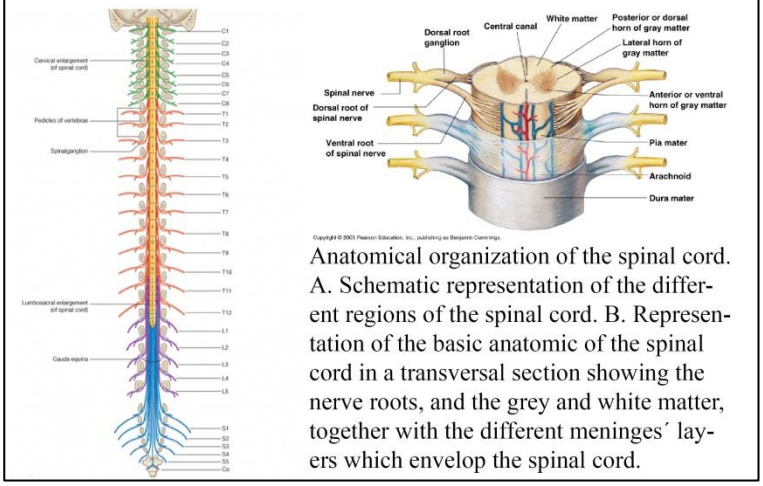
All these descending pathways have three common functions within the motor system: (a) The most distinctive function of the descending motor pathways is the control of voluntary movement. These movements are initiated in the cerebral cortex, and the motor commands are transmitted to the musculature through a variety of descending pathways, including the corticospinal tract, the

rubrospinal tract, and reticulospinal tracts. (b) Modulate the reflex circuits in the spinal cord. The adaptiveness of spinal reflexes can change depending on the behavioural context; sometimes the gain (strength) or even the sign (extension vs. flexion) of a reflex must be changed in order to make the resulting movement adaptive. (c) Muscle contraction consists in the coordination of different types of motor neurons innervating the contracting muscle (see below), in order to elaborate a proper movement those motor neurons must be coordinated, the so called alpha-gamma coactivation, and the muscle spindle sensitivity must be adjusted properly in all phases of the contraction (gamma bias).

Spinal Cord, Reflexes and Reciprocal Inhibition

Spinal cord anatomy and circuits (Snell R. 2009. Clinical neuroanatomy, 9th Edition)

Figure 2



Anatomical organization of the spinal cord. A. Schematic representation of the different regions of the spinal cord. B. Representation of the basic anatomic of the spinal cord in a transversal section showing the nerve roots, and the grey and white matter, together with the different meninges´ layers which envelop the spinal cord.

The spinal cord is the most important structure between the body and the brain. The spinal cord extends from the foramen magnum where continues with the medulla to the level of the first or second lumbar vertebrae. It is a vital link between the brain and the body, and from the body to the brain. Two consecutive rows of nerve roots emerge on each of its sides. These nerve roots join distally to form 31 pairs of spinal nerves. The spinal cord is a cylindrical structure of nervous tissue composed of white and gray matter, is uniformly organized and is divided into four regions: cervical (C), thoracic (T), lumbar (L) and sacral (S), (see figure 2), each of which is comprised of several segments. The spinal nerve contains motor and sensory nerve fibers to and from all parts of the body. The cord is sheathed in the same three meninges as is the brain: the pia, arachnoid and dura. The dura is the tough outer sheath, the arachnoid lies beneath it, and the pia closely adheres to the surface of the cord (See Figure 2). The spinal cord is attached to the dura by a series of lateral denticulate ligaments emanating from the pial folds. In this document the meninges layers play an important role as it is the target of one of the treatment against spasticity, Baclofen pumps, where baclofen is injected directly into the Arachnoid space to provide a local and specific targeting of the spinal cord by Baclofen.

A transverse section of the adult spinal cord shows white matter in the periphery, gray matter inside, and a tiny central canal filled with Cerebrospinal Fluid at its centre. Surrounding the canal is a single layer of cells, the ependymal layer. Surrounding the ependymal layer is the gray matter – a region containing cell bodies – shaped like the letter “H” or a “butterfly”. The two “wings” of the butterfly are connected across the midline by the dorsal gray commissure and below the white commissure (See Figure 3). The shape and size of the gray matter varies according to spinal cord level. At the lower levels, the ratio between gray matter and white matter is greater than in higher levels, mainly because lower levels contain less ascending and descending nerve fibers.

The distribution of cells and fibers within the gray matter of the spinal cord exhibits a pattern of lamination. The cellular pattern of each lamina is composed of various sizes or shapes of neurons (cytoarchitecture) which led a new classification based on 10 layers (laminae). This classification is useful since it is related more accurately to function than the previous classification scheme which was based on major nuclear groups (see Figure 3). Surrounding the gray matter is white matter containing myelinated and unmyelinated nerve fibers. These fibers conduct information up (ascending) or down (descending) the cord. The white matter is divided into the dorsal (or posterior) column (or funiculus), lateral column and ventral (or anterior) column (see Figure 3). Three general nerve fibers types can be distinguished in the spinal cord white matter: 1) long ascending nerve fibers originally from the column cells, which make synaptic connections to neurons in various brainstem nuclei, cerebellum and dorsal thalamus, 2) long descending nerve fibers originating from the cerebral cortex and various brainstem nuclei to synapse within the different Rexed layers in the spinal cord gray matter, and 3) shorter nerve fibers interconnecting various spinal cord levels such as the fibers responsible for the coordination of flexor reflexes. Ascending tracts are found in all columns whereas descending tracts are found only in the lateral and the anterior columns.

Information from the skin, skeletal muscle and joints is relayed to the spinal cord by sensory cells located in the dorsal root ganglia. The dorsal root fibers are the axons originated from the primary sensory dorsal root ganglion cells. Each ascending dorsal root axon, before reaching the spinal cord, bifurcates into ascending and descending branches entering several segments below and above their own segment. The ascending dorsal root fibers and the descending ventral root fibers from and to discrete body areas form a spinal nerve. There are 31 paired spinal nerves. The dorsal root fibers segregate into lateral and medial divisions. The lateral division contains most of the unmyelinated and small myelinated axons carrying pain and temperature information to be terminated in the Rexed laminae I, II, and IV of the gray matter. The medial division of dorsal root fibers consists mainly of myelinated axons conducting sensory fibers from skin, muscles and joints; it enters the dorsal/posterior column/funiculus and ascend in the dorsal column to be terminated in the ipsilateral nucleus gracillis or nucleus cuneatus at the medulla oblongata region, i.e., the axons of the first-order (1°) sensory neurons synapse in the medulla oblongata on the second order (2°) neurons (in nucleus gracillis or nucleus cuneatus). In entering the spinal cord, all fibers send collaterals to different Rexed lamina.

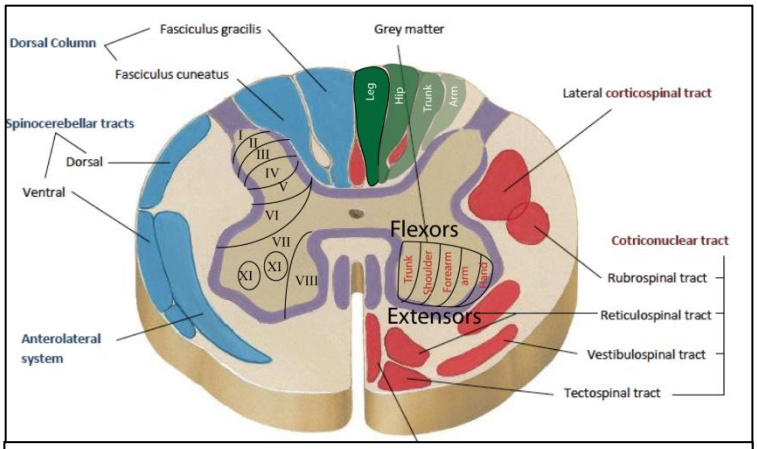


Figure 3. Laminar and nuclear organization in the spinal cord. The white matter is composed by several ascending and descending fascicles tracts distributed in the dorsal, medial and ventral parts of the white matter. The nuclei of the different projection neurons and interneurons are organized in several nuclei and laminae constituting the somatotopic representation map in the spinal cord.

Axons entering the cord in the sacral region are found in the dorsal column near the midline and comprise the fasciculus gracillis, whereas axons that enter at higher levels are added in lateral

positions and comprise the fasciculus cuneatus. This orderly representation is termed “somatotopic representation” (see Figure 3).

Reflexes and type of reflexes.

The definition of a reflex may be expressed as follows “an involuntary and nearly instantaneous movement in response to a stimulus” (Purves et al., 2001, Neuroscience 2nd Edition). A sense of body position is necessary for adaptive motor control. In order to move a limb toward a particular location, it is imperative to know the initial starting position of the limb, as well as any force applied to the limb. Muscle spindles and Golgi tendon organs provide this type of information. In addition, these receptors are components of certain spinal reflexes that are important for both clinical diagnoses as well as for a basic understanding of the principles of motor control and reciprocal inhibition.

Several sensory receptors within the muscle report the status of it during movement and in repository state. The main receptors are the muscle spindles, modified muscle fibers embedded within the extrafusal fibers (the main responsible of the muscle contractions). Their definition and physiological properties are beyond the scope of this document, for more information the reader is encourages to find information in the Boron W. and Boulpaep E., 2009.

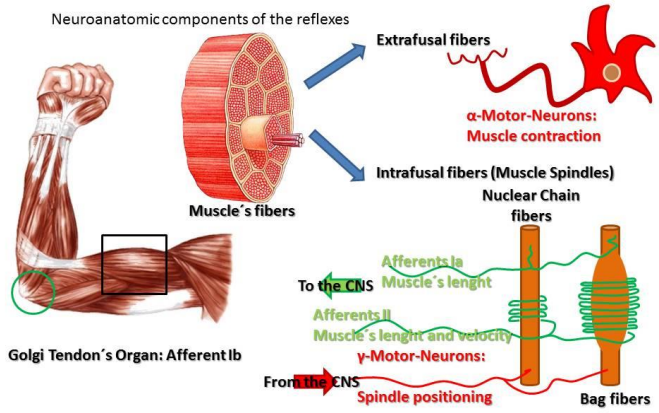


Figure 4. Representation of the sensory organs in the skeletal muscle. Muscle spindles are innervated by different kinds of neurons, such as motor neurons and sensory neurons, they report the muscle´s status to the Central Nervous System of the muscle length and velocity.

Medical Physiology, 2nd Edition). There are three different types of muscle spindles or intrafusal fibers (Nuclear chain, Static Nuclear Bag and Dynamic Nuclear Bags fibers) and each of them is innervated by three types of neurons, i) γ-Motorneurons coming from the ventral horn of the spinal cord and constituting the motor unit, and ii) Sensory afferent neurons, having two groups the primary afferents (Ia afferents) and the secondary (II afferents). Because of their patterns of innervation onto the three types of intrafusal fibers, Group Ia and Group II afferents respond differently to different types of muscle movements. These receptors provide information about the velocity and length (Nuclear bags) or just the position and length (Nuclear Chain fibers). Another sensory organ is the Golgi Tendon Organ, a specialized receptor that is located between the muscle and the tendon. Unlike the muscle spindle, which is located in parallel with extrafusal fibers, the Golgi tendon organ is located in series with the muscle and signals information about the load or force being applied to the muscle.

There are different types of reflexes, here we will illustrate some of them pointing out the importance of the reciprocal inhibition needed to coordinate the muscle agonist-antagonist movement to achieve a successful contraction of the body limbs.

The first type of reflexes is the **Myotatic reflex or stretch reflex**, this reflex is started by an activation of the Ia afferent due to a sudden muscle stretch activating the muscles spindle, this causes that the afferent fiber Ia sends a signal towards the spinal cord through the dorsal horn, the afferent will trigger a monosynaptic activation of the alpha motor neuron that causes the muscle to contract. As a result, the stretch of the muscle is quickly counteracted, and the muscle is able to counteract the stretch action and maintain its position. A major role of the myotatic reflex is the maintenance of posture. If one is standing upright and starts to sway to the left, muscles in the legs and torso are stretched, activating the myotatic reflex to counteract the sway. In this way, the higher levels of the motor system are able to send a simple command ("maintain current posture") and then be uninvolved in its implementation. The lower levels of the hierarchy implement the command with such mechanisms as the myotatic reflex, freeing the higher levels to perform other tasks such as planning the next sequence of movements.

A second type of reflex involves the Golgi tendon organ and is known as the **autogenic inhibition reflex**. When tension is applied to a muscle, the Group Ib fibers that innervate the Golgi tendon organ are activated. These afferents have their cell bodies in the dorsal root ganglia, and they project into the spinal cord and synapse onto *an interneuron* called the Ib inhibitory interneuron. This interneuron makes an inhibitory synapse onto the alpha motor neuron that innervates the same muscle that caused the Ib afferent to fire.

The third and last type of reflex is the **flexor reflex** and it is initiated by proprioceptor (receptors informing the body about posture) or nociceptors (pain receptors) which sends information through the afferent fibers type III to the spinal cord innervating different excitatory interneurons at different levels to activate different muscles in a coordinated fashion to trigger the hip flexor muscles in order to for example withdraw the limbs from a painful stimulus. To illustrate this reflex we can think in accidentally touching a hot stove or a sharp object, as we withdraw our hand even before we consciously experience the sensation of pain. This quick reflex removes the limb from the damaging stimulus more quickly than if the pain signal had to travel up to the brain, be brought to conscious awareness, and then trigger a decision to withdraw the limb.

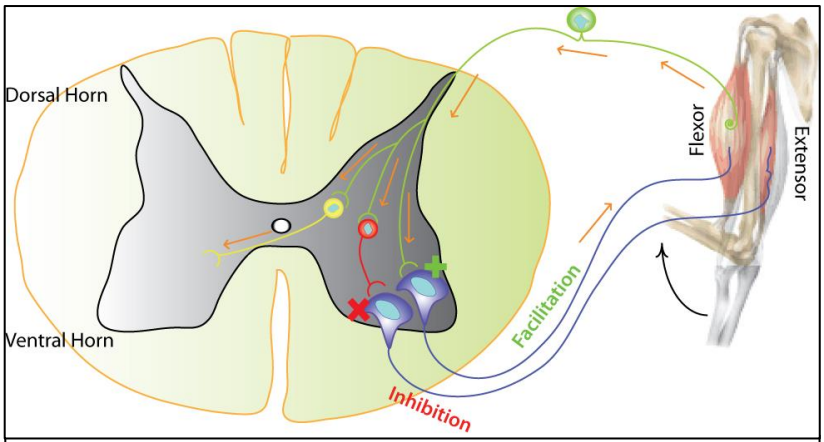


Figure 5. Principles of the reciprocal inhibition. After the muscle (flexor) is stretched the afferent Ia (green) sends a signal to the spinal cord, where it will perform synapse with an alpha-motorneuron and an interneuron. The alpha-motorneuron inervates the same muscle as the Ia afferent (agonist muscle) and achieves contraction of that muscle, while the interneuron inhibits the alpha-motorneuron inervating the antagonist muscle (Extensor), to avoid co-contraction and a successful flex movement of the arm.

In all these reflexes we have described the involvement of one sensory afferent (coming from the muscle spindle) and the motor neuron innervating the same muscle. But any movement involves more than just one muscle, as to achieve a proper movement it is needed to activate an agonist

muscle (responsible of the movement) and to inhibit an antagonist one (responsible of the movement in the opposite direction), this is the very basic principle of the *reciprocal inhibition*. Joints are controlled by two opposing sets of muscles, extensors and flexors, which must work in synchrony. Thus, when a muscle spindle is stretched and the stretch reflex is activated, the opposing muscle group must be inhibited to prevent it from working against the resulting contraction of the homonymous muscle (see Figure 5). This inhibition is accomplished by an inhibitory interneuron in the spinal cord. The Ia afferent of the muscle spindle bifurcates in the spinal cord. One branch innervates the alpha motor neuron that causes the homonymous muscle to contract, producing the behavioural reflex. The other branch innervates the Ia inhibitory interneuron, which in turn innervates the alpha motor neuron that synapses onto the opposing muscle. Because the interneuron is inhibitory, it prevents the opposing alpha motor neuron from firing, thereby reducing the contraction of the opposing muscle. Without this reciprocal inhibition, both groups of muscles might contract simultaneously and work against each other.

Worth of mention in this chapter is the fact that all these different synaptic circuits involved in the reflexes can be measured using a relative simple techniques, easy to use in neurology settings. Furthermore these measure techniques have been extensively investigated and relevant factors are well understood when applied to spasticity measurements, nevertheless these techniques lack of correlation with clinical scales[11]. We will make a short mention about the H-reflex (Hoffmann Reflex) and the T-reflex (Tendon Reflex).

The H-Reflex first shown by Piper in 1912 and described in detail by Hoffmann in 1918 is a low threshold, spinal reflex that can be elicit by electrical stimulation of a mixed peripheral nerve[12]. Basically this measurement bypasses the muscle spindle and exerts direct stimulation at a low threshold of the big diameter sensory afferent fibers, this stimulation will travel towards the spinal cord and do synapsis with the motor neuron of that same muscle eliciting a contraction response. If the intensity of the stimulus is increase the lower diameter motor neurons fibers will be also stimulated inducing a response called M-wave (no synapses done). So the H-Reflex serves to measure the synapsis involved in the spinal cord reflexes. The T-reflex or phasic stretch reflex, is the mechanical counter part of the H-reflex, tapping a distal tendon stimulates the Ia afferent fibers (stretch reflex) sending the signal to the spinal cord and where they synapse with the motorneurons eliciting a short contraction[13]. Reciprocal inhibition can be assessed using the ratio between H-reflex under stimulation divided by H-reflex during normal conditions[14,15]. As we will see later these parameters can also give qualitative information about the spasticity level in patients.

The Upper Motor Neuron Syndrom (UMNS)

It is defined as alterations in the motor system at any of its levels having as a consequence the loss of voluntary and fine tuning movements. The UMNS has two classical distinctions in terms of its signs and symptoms, also referred as components[16]:

Positive components	Negative components
Exaggerated tendon reflexes	Spastic co-contractions
Release reflexes	Motor weakness
Babinski sign	Slowed movements
Clonus	Loss of Dexterity
Spastic dystonia	Loss of selective motor control
Spasticity	

Table 1. Following a UMN lesion a person will present with a combination sensory-motor signs and symptoms that are broadly classified as negative phenomena (characterized by a reduction in voluntary motor activity) and positive phenomena (characterized by increased levels of involuntary motor activity)[17,18]

How do these positive symptoms come about? They can be divided into three main areas. Firstly, spinal reflexes: Abnormal processing of spinal reflexes contributes to most of the positive features of the UMNS. They are all afferent dependent, relying upon some sort of sensory feedback. The third group of positive UMN signs are the various disorders of voluntary muscle movements, although there is much overlap with the negative signs/component, we will focus mainly on the positive side, that is, features characterized by muscle over activity.

Lesions in the CNS leading to a UMNS

Stroke and Cerebral Palsy: Alteration of descending pathways, affecting mainly to corticospinal and Rubrospinal descending pathways.

Cerebral Palsy (CP) described as a range of non-progressive syndromes of posture and motor impairment as a common cause of disability in childhood, occurring before of within the 2 years of birth[19,20]. This disorder results from various insults to different areas within the developing nervous system, which partially explains the variability of clinical findings[21]. The motor impairments result from various neurological deficits[20]. CNS pathology associated with cerebral palsy includes: CNS haemorrhage, mechanical spinal cord or brainstem damage, deep CNS hypoxia; cerebral cortex hypoxia and transient or irreversible ischemia resulting in cell necrosis. The unique metabolic demands of the basal ganglia in the foetus at 38-40 weeks create “selective” vulnerability that can result in dystonia or movements disorders[22-24]. Although causes of CP have been always associated to complications in the delivery, recently more studies point the possibility of a genetic background and hereditable polymorphs as one of the causes of the CP[25,26].

Blood vessels that carry blood to the brain from the heart are called arteries. The brain needs a constant supply of blood, which carries the oxygen and nutrients it needs to function. Each artery supplies blood to specific areas of the brain. A **stroke** occurs when one of these arteries to the brain is either blocked or bursts. As a result, part of the brain does not get the blood it needs, so it starts to die. A transient ischemic attack (TIA) occurs when the blood supply to the brain is blocked for a short

time. When this happens, the brain temporarily malfunctions. There are several kinds of strokes (more information available at ww.stroke.org):

Ischemic Stroke: Produced by the formation of blood clots which can block arteries and cut off blood flow, a process called ischemia. An ischemic stroke can occur in two ways: embolic and thrombotic strokes. (i) In an embolic stroke, a blood clot forms somewhere in the body (usually the heart) and travels through the bloodstream to your brain. Once in your brain, the clot eventually travels to a blood vessel small enough to block its passage causing the stroke (embolus). (ii) In the second type of blood-clot stroke, blood flow is impaired because of a blockage to one or more of the arteries supplying blood to the brain. The process leading to this blockage is known as thrombosis.

Blood-clot strokes can also happen as the result of unhealthy blood vessels clogged with a build-up of fatty deposits and cholesterol. The body regards these build-ups as multiple, tiny and repeated injuries to the blood vessel wall, reacting to these injuries forming clots. Two types of thrombosis can cause stroke: large vessel thrombosis and small vessel disease (or lacunar infarction.)

Hemorrhagic Stroke: Strokes caused by the breakage or "blowout" of a blood vessel in the brain are called hemorrhagic strokes. The medical word for this type of breakage is hemorrhage. Hemorrhages can be caused by a number of disorders which affect the blood vessels, including long-standing high blood pressure and cerebral aneurysms. An aneurysm is a weak or thin spot on a blood vessel wall. These weak spots are usually present at birth. Aneurysms develop over a number of years and usually don't cause detectable problems until they break. There are two types of hemorrhagic stroke: subarachnoid and intracerebral.

Due to the advances of neuroscience that enabled the better understanding of brain plasticity mechanism underlying the phenomena of motor and cognitive recovery and a better integration of the learning theories in the rehabilitation theories, the methods and means available for the rehab of stroke patients has considerably improved[27].

Spinal Cord lesions (Injuries) or SCI. Disruption of the spinal cord circuits and/or descending tracts located in the dorsolateral and medio-ventral regions of the white matter.

It is an insult to the spinal cord resulting in a change, either temporary or permanent, in the cord's normal motor, sensory and/or autonomic function. Patients with spinal cord injury usually have permanent and often devastating neurologic deficits and disability. Common causes of damage are trauma or disease (transverse myelitis, polio, spina bifida, Friedreich's ataxia, etc.). The spinal cord does not have to be severed in order for a loss of function to occur. Depending on where the spinal cord and nerve roots are damaged, the symptoms can vary widely, from pain to paralysis to incontinence (Lin et al., 2002. Spinal Cord Medicine: Principles and Practice; Kirshblum et al. 2003. Spinal Cord Medicine). The American Spinal Injury Association (ASIA) has published a list of different categories based in the extend of the injury and the impairment resulted from it[28,29]:

A = Complete: No sensory or motor function is preserved in sacral segments S4-S5

B = Incomplete: Sensory, but not motor, function is preserved below the neurologic level and extends through sacral segments S4-S5

C = Incomplete: Motor function is preserved below the neurologic level, and most key muscles below the neurologic level have a muscle grade of less than 3

D = Incomplete: Motor function is preserved below the neurologic level, and most key muscles below the neurologic level have a muscle grade that is greater than or equal to 3

E = Normal: Sensory and motor functions are normal

Definitions of complete and incomplete spinal cord injuries are bases in the ASIA and SS (Sacral-Sparing) classifications[30]. *Complete*: Absence of sensory and motor functions in the lowest sacral segments; *Incomplete*: Preservation of sensory or motor function below the level of injury, including the lowest sacral segments.

Neurodegenerative diseases. This group of disease involved Huntington and Parkinson diseases (Alzheimer is related to cognitive areas such the hippocampus) , characterized for a progressive cell death in some of the main motor areas in the brain, especially at the level of Basal Ganglia. Although some other diseases like hemiballismus or Cerebellum´s disorders are also affecting motor control we are not going to describe them fully in this chapter.

Huntingston´s disease: It is an incurable genetic (autosomal dominant mutation) neurodegenerative disorder that leads to motor (it is characterized by a continuous, choreiform movements of the body (especially the limbs and face) and cognitive (dementia) decline. It is caused by an expanded polyglutamine (abnormally large number of repeats of the nucleotide sequence CAG on chromosome 4) tract within the Huntingtin gene, which translates into a toxic mutant of this protein[31]. This results in a neuronal death in the Striatum (basal ganglia) of inhibitory cells in charge of inhibiting the excitatory outputs coming from the thalamus towards the cortex. As a result the cortex gets too much excitatory input disrupting its normal functioning and sending involuntary movements' commands to the brain stem and the spinal cord.

Parkinson's disease: results from the death of dopaminergic neurons in the substantia nigra pars compacta; characterized by a resting tremor, but the most debilitating symptom is severe bradykinesia or akinesia[32,33]. In advanced cases, patients have difficulty initiating movements, although involuntary, reflexive movements can be normal. The loss of neurons in the substantia nigra projecting into the basal ganglia means the loss of both excitatory and inhibitory inputs and therefore upsets the fine balance of excitation and inhibition reducing the excitation of the moor cortex.

Spinal reflexes as the major responsible for most of the positive features in the UMNS.

Hyperactive spinal reflexes mediate most of the positive features in the UMNS. All diseases and lesions described above resulted in some kind of unbalance of the supraspinal inhibitory and excitatory inputs, producing a state of disinhibition of the spinal reflexes[34]. The dysregulation of the spinal reflexes can be categorized into: i) disinhibition of the existing normal reflexes, which are involved in walking and all other movements. One form is the propiospinal phasic stretch reflex, also known as the tendon jerks (inflicting enough pressure under the knee-cap can trigger this reflex) in normal conditions, but within the UNMS it is hyper exaggerated and evolving to a hyperactive phasic

stretch reflex known as clonus. ii) the nociceptive reflexes including the flexor withdrawal reflex, producing flexor spasm (the normal way this reflex works would be when in contact with something potentially dangerous for the body, t.ex a sharp object or fire) an immediate response from the muscles of the limb takes place withdrawing it from the potential harmful stimulus. iii) The last form of reflexes would be enclosed in the cutaneous reflexes related to the first two types of reflexes.

Spasticity

Spasticity, a neurological impairment, is a common, but not an inevitable, consequence of the UMNS. It is one of many sensory-motor signs and symptoms that may be present following an UMN lesion (see table 1 in the UMNS section). Spasticity is commonly defined using the terms expressed by Lance (1980) as …. *motor disorder characterized by a velocity dependent increase in the tonic stretch reflex (muscle tone) with exaggerated tendon jerks, resulting from the hyper excitability of the stretch reflex, as one component of the upper motor syndrome*….[35] Although this is quoted as a the most common definition of spasticity, other researchers like Denny-Brown[36] and Tardieu[37] have also provided similar descriptions. Although this definition of spasticity is commonly accepted and in used nowadays, several authors have criticized Lance´s definition as narrow and limiting under clinicians view[38,39] and researchers claim that the phenomena seen in the UMNS are not related to the original definition[40,41]. Paydan and colleagues(2005)[42] claim that Lance´s definition although commonly used has never been fully validated …*there is insufficient evidence in the literature to support the hypothesis that the abnormal muscle activity observed in spasticity results exclusively from stretch reflex hyperexcitability*…. This controversy around the definition of spasticity does not set a major hinder in the study and treatment of spasticity, on the contrary it indicates that due to advances in the neurobiology and neuroscience fields, we acquire a more profound view and deeper knowledge of the cell biology behind this phenomena (see table 2), which in turn will lead us to a better approaches and treatments against this positive feature of the UMNS.

Pathophysiology of spasticity[16]
Supraspinal pathways
Release of brain stem reflexes from cortical inhibition
Overactivity of non-adrenergic pathways from locus coeruleus
Overactivity of serotoninergic pathways from raphe nucleus
Spinal cord
Loss of recurrent inhibition, mediated by motor axon collaterals and Renshaw cells
Loss of reciprocal inhibition, mediated by antagonistic muscle spindle afferents
Reduced inverse stretch reflex, mediated by Golgi tendon organs
Reduced presynaptic inhibition of muscle spindle afferents
Spinal motor neurone
Denervation super sensitivity
Collateral sprouting
Muscles and joints
Shortening of sarcomeres
Loss of elastic tissue
Fibro-fatty deposits in muscles and tendons

Table 2. Advances in research have allowed us to identify the functional changes associated with or resulting from UMNS developing spasticity.

Spasticity is a fairly common problem in persons who sustain a spinal cord injury (SCI), Cerebral Palsy and stroke (see table 3). The muscles in the arms, legs, and the trunk are often painful, resistant to movement, difficult to control, and prone to spasms or involuntary movements. Spasticity may be used to help with transfers and walking, or may help keep the muscles from decreasing in size. However, there are problems that result from spasticity. Long-term spasticity can lead to decreased range of motion (ROM), prevent safe positioning, limit mobility, and impede hygiene. Spasticity can

also lead to increased discomfort and pain. Spasticity is actually a combination of problems. Specifically, spasticity is not just defined as resistance to movement when an arm or leg is moved quickly. Some persons with spasticity also have spasms and clonus (repeated movement of a body part when positioned with the muscle stretched). It is not yet clear which treatment is best for these different aspects of spasticity. While frustrating for some, the presence of spasticity can be viewed as beneficial for others. For instance, spasticity can aid in maintaining muscle bulk and blood circulation, both of which can prevent pressure sores. Spasticity can also be used to aid in mobility, such as for transfers and walking. However, the less desirable effects of spasticity, such as decreased range of motion (ROM), interference with positioning, mobility, and hygiene, and increased discomfort and pain often outweigh those that are beneficial, making intervention necessary. Clinical interventions include pharmacological approaches, as well as rehabilitation, surgical, and alternative medicine approaches (See below).

Diseases presenting predominately as spasticity
Spinal cord compression[43,44]
Primary progressive multiple sclerosis[45]
Motor neurone disease[34]
Spinal vascular malformations
Hereditary spastic paraparesis
Subacute combined degeneration of the cord
Human T-lymphotropic virus myelopathy

Table 3. Some of the diseases that include as positive feature spasticity

Sheean (2002)[34] described in a precise manner the key points about spasticity, pointing out the following features:

1. Spasticity seen as a tonic stretch reflex
2. Spasticity might be mediated by Ia afferents (sensory fibers coming from the muscle spindles, see above)
3. Velocity (and length) dependent
4. Dynamic but there is also a static component (keeping the muscle stretched does not reduced contraction in many cases despite the Lance´s definition)
5. Muscle spindles are not more sensitive in a person with spasticity, it is what happens in the spinal cord what gives the outcome, pointing out spasticity as a clear spinal phenomenon.

Outcome measures of spasticity. Johnson (2002)[46] stated that reviews and book chapters about clinical scales for spasticity and associated clinical phenomena, concentrate mainly on the most frequently used scales and some of their psychometric characteristics[47-49]. Platz and colleagues (2005)[50] describe in an extensive manner a total of 24 clinical scales that assess spasticity and/or related phenomena as well as 10 scales to rate “active function” and 3 scales for “passive function” associated with spasticity. One of the main conclusion drawn in their review of electronic databases including up to 4151 references (90 of them were used in the actual review) was that every scale has it major benefits and drawbacks depending of the circumstances used as well as the treatment and pathology, but Ashworth and modified Ashworth scales (MAS) seemed to achieved the highest reliability although not in all circumstances[11]. One of the main objectives of the scales is their ability to report changes upon treatments and that these changes have correlation with the clinical

outcomes, at the same time the inter-rater reliability must be achieve high levels in order to be applied in different cases.

Here we will report different scales available following their psychometric properties: scales assessing tone (resistance to passive motion); scales assessing range of motion and posture and scales for clinical phenomena related to spasticity. Here we will just point out those scales applied in a general fashion without going into deeper detail for those scales rating specific movements. For more detailed information the reader is encouraged to further readings[46,50].

Name of the scale	References	Comments
Ashworth scale	51,52	
Modified Ashworth scale (MAS)	53,54	
Velocity-corrected MAS		
Muscle tone scale		
Modified Tardieu scale	55	
"Spasticité"		Multiple-item scale
VAS for tone (clinical rate)	56	
VAS for tone (patient)	44	Higher reliability compared to the VAS scale assessed by clinicians
Tone assessment scale		
Range of motion (ROM)		Can be performed with goniometer and/or visually
Spasm severity scale		
Spasm frequency scale		
Clonus score		

Table 4. Scales for assessment of spasticity and clinical phenomena.

Among all the scales cited above (table 4), Ashworth scale, MAS and Modified Tardieu scales are the ones having less variability between assessment, representing a high inter-rate value and reliability. Concerning to the VAS (Visual Analogue Scale), the one applied to the patients is more reliable compare to the VAS performed by clinicians, assuming the patient can answer to the presented items in a logical fashion. Ashworth and MAS scores are closely associated with other signs of the UMNS, moderate association with reflex-related Electromyography (EMG) and a stronger association with resistance to passive movement. One of the major cons regarding to the MAS is the difficulty of the assessment of scores 1, 1+ and 2, as may fail to represent different levels of resistance to passive movement, resulting in a lower interrater reliability[57,58]. Worth of mention that the modified Tardieu scale is suitable to tract changes of spasticity upon therapeutic treatment in children with CP.

Name of scale	Comments
Grip strength	
Muscle strength grading (MRC)	
Active ROM	Range of Motion
Gait analysis[59]	
Fugl-Meyer[60]	
QUEST	Quality of Upper Extremities Skills
GMFM	Gross Motor Function Measure
PEDI, self-care score	Paediatric Evaluation Disability Inventory
Barthel Index	

Table 5. Scales assessing the active function.

Regarding to active function scales (table 5), they measure the capacity to move the body or one of its part actively. Note that these scales are related somehow with those showed above, especially important is the higher correlation that some of these scales show with the Ashworth and Modified Ashworth scales (Gait analysis, Fugl-Meyer, QUEST, GMFM, PEDI and Barthel index). One of the most used and common scales to measure active function is the GMFM together with the Manual Ability Classification System or MACS, especially in children with CP[24].

Last but not least, there are assessments of passive function measure with the following scales: Hygiene score, Disability scale and Carer burden scale. These scales are more into the Quality of Life scales and scores as they represent the impact of spasticity in the daily life, they are completely subjective scales and results can vary greatly between individuals and within the same patient depending on the date and psychological predisposition of the patient when the test are perform (more information will be displayed in later chapters of this document).

Management options/Treatments

Spasticity frequently impairs one's mobility, positioning, comfort, care and ability to perform activities of daily living. Successful management of spasticity requires the expertise of a well-integrated team of clinicians. Commonly used management strategies for spasticity include:

- Oral medications, particularly for those with spinal cord injury
- Orthopaedic procedures to correct deformities resulting from spasticity or to augment the effects of other treatments
- Bracing and splinting
- Muscle stretching, positioning and movement exercises

These strategies have been grouped as common or classical treatments against spasticity, however the list is more extensive as several other options are available:

- Injected medications: Mainly oriented to synaptic blockade at the Neuro Muscular Junction, here the main and more extensively used are the Botulinum Toxins
- Intrathecal Baclofen Pump: A major surgery procedure where a pump is inserted in the abdominal cavity and Baclofen is injected directly into the Nervous system through the arachnoid space in the meninges
- Selective Dorsal Rhizotomy: Also a major surgical procedure characterize by the excision of the afferent sensory inputs into the spinal cord.
- Electro-Therapy: A non-invasive method based in the electric stimulation of either muscles or nerves.

In the spasticity treatments it is common that two or more treatments are combined in other to improve the patient's motor functions, and in some cases it has been reported additive effects between different therapies[61,62]. In this part we will mainly focus on the most common used therapies emphasizing differences, conveniences and disadvantages together with the impact in the quality of life and function of the patients.

Pharmacological methods.

Diazepam was the first one used and Oral Baclofen is also a highly used drug for the spasticity treatment. However due to their multiple and potentially dangerous side effects, these compounds will be omitted in this document in favour of the most specific and powerful treatment of intrathecal baclofen. Nevertheless we do provide a brief list of some references regarding the use of these compounds; these articles constitute a review and meta-analysis of several of the oral medications used in the treatment of spasticity together with other forms of medical management[63-65]

Intrathecal Baclofen (ITB): One of the major advantages of ITB compared to the oral administration is the lack of many side effects, as with this system the drug administration is performed locally, besides the concentration needed to obtain same results as the oral medication is just 1% compare to the orally administered Baclofen[63]. The intrathecal baclofen is indicated for patients with severe spasticity and GMFCS scores of IV[66]. Its mechanism of action is exerted at receptor level, acting on the metabotropic receptor GABAb which in turn induces inhibition of the synaptic transmission opening K+ channels and thus hyperpolarization the neuron avoiding it to trigger actions potentials[67].

This means and inhibition of the reflex arc as all neurons in the spinal cord stop functioning and therefore stop sending signals towards the muscle.

This method is a proven procedure that ensures a reduction in the level of spasticity rated as a decrease in the Ashworth scales and MAS as well as an increase in Life Satisfaction questionnaires and Quality of Life scores[68-70]. Among other advantages this system is highly controllable and it also affects Pain-relieving (as it inhibits all signals produced at the spinal level). However as a major surgery process it involves risk of infections during the procedure of pump implantation varying from 1[71] to 9%[72]. It is also been reported a high rate in incidents per recipient year follow-up up to 0,48, The system itself is highly reliable, but an organized follow-up program is necessary to cope with the procedure-related problems such as catheter dislodgement or other complications[73]. Recently, Awaad and colleagues (2012)[74] reported complications of intrathecal baclofen pump installation where 22 out of 44 patients needed to perform several revision and several failures were detected during the follow up time.

On the other hand even there are not so many side effects compare to the oral medication, however there are still some side effects regarding the action mechanism of the baclofen at the spinal cord level: weakness, hypotension, possible overdose and behavioural changes. We have also to take in account the cost/effectiveness ratio of ITB. As it has been said before Baclofen increase the Quality of life Score, but this increase comes at expense of an increased price. The net result is an incremental cost-effectiveness ratio of $42.000 per quality-adjusted life-year, well within the $50 000 to $100 000 range[75]. The authors consider these results as "…..*widely accepted as offering good value for the money."* Its efficacy has been also evaluated as cost/success ratio, having ITB as a high success treatment it cost/success ratio is elevated to 75.204£[76]. Some other reports state a total price of 28.473$ the first year but it also reports savings originated from withdrawal of oral medication (1.950-2.800$), job preservation and avoidance or delay of admission to a nursing home (1.047-5.814$)[77].

In summary ITB is an effective method against spasticity as it reduces Ashworth scale scores and increases the Quality of Life, although it entails risk of infections which can discourage a long-term treatment, constant refill of the pump (with additional cost) and some adverse side effects. Nevertheless the main drawback of ITB is related to the price.

Chemodernervation.

In the same fashion as the pharmacological methods, mention will be done to Ethanol and phenol injections in muscles, although no deep analysis of those will be done in favour of the action mechanism exerted by the more well know and more commonly used Botulinum toxins.

Alcohol and phenol are very old approaches to achieve focal chemodernervation on spastic muscles[78]. They are considered neurolytic agents, as their action mechanism is based in denaturalization and non-selective tissue destruction, including nerve coagulation and muscle necrosis. The targets are mainly distal muscles and its action is achieved through two different approaches: motor nerve block (low volume injections) and motor point block (multiple injections at different doses, grading the effect on the muscle). But as said before it is not a safe method and there are significant side-effects.

Botulinum toxins (BoTN) are a widely used pharmacological treatment used against local spasticity. It is achieve by injection of the toxins into the muscle where it will block the release of the neurotransmitter Acetylcholine into the synaptic space and therefore inhibiting the transmission of the axon signal into the muscle abrogating completely the muscle contraction. There are seven different neurotoxins (labelled as type A, B, C (C1, C2), D, E, F and G) which are structurally similar but target different antigens (target proteins). Types A, B and E (rarely F) cause toxicity in humans whereas types C and D affects animals[79]. All different subtypes target the synaptosome, a protein complex in charge of mediate the fusion of vesicles within the cell to their membranes in order to secrete a specific compound within the vesicle. In this document we will not address the different subtypes and targets, as is far from the scope of botulinum toxins as spasticity treatment, whoever Jankovic (2004) describe the pharmacology and action mechanism of the different subtypes in case the reader is interested[80].

There are available different types of commercially BoNT, each of them is employed under different circumstances and treatments (information retrieve from Medscape (http://www.emedicine.medscape.com/article/325451-overview#a1):

1. OnabotulinumtoxinA (Botox®, Botox Cosmetic®):
   - ✓ Botox® - Cervical dystonia, severe primary axillary hyperhidrosis, strabismus, blepharospasm, neurogenic detrusor overactivity, chronic migraine, upper limb spasticity
   - ✓ Botox Cosmetic® - Moderate to severe glabellar lines, moderate to severe lateral canthal lines, known as crow's feet
2. AbobotulinumtoxinA (Dysport®) - Cervical dystonia, moderate to severe glabellar lines.
3. IncobotulinumtoxinA (Xeomin®) - Cervical dystonia, blepharospasm, moderate to severe glabellar lines.
4. RimabotulinumtoxinB (Myobloc®) - Cervical dystonia

Many reports have stated the positive effects of BoNT in the treatment of spasticity, however Moore (2002) warns about the fact that many of those studies are open, uncontrolled studies, while the BoTN benefits is also present but scarce and less convincing from randomized controlled trials (RCT) and that could be due to a variety of technical reasons[81]. Since then, more RCT have been accumulating positive effects in spasticity, but it is still a concern the lack of more data coming from this high level empirical studies and even if BoTN has positive effects in the treatment of spasticity, the effect in functionality are still somehow controversial, due to the lack of effect of BoNT in the muscle intrinsic properties[82]. This is the main reason that has driven some authors to claim that BoTN treatment works best in combination with other forms of therapy[83]. Garcia Salazar and colleagues (2014)[82] performed a systematic review on the effects of BoTN in the treatment of spasticity and functional recovery, showing in the 17 studies analysed the effect of BoTN were evident in the reduction of spasticity, but it did not however increase functionality in the treated muscles. In a two big studies performed over more than 500 and 200 BoNT treated patients respectively, the goal attachment scaled was scored up to 51%, which lead the authors to claim that the efficacy of the BoTN was proven, nevertheless the treatments must be carefully planned and evaluated the risk of long term treatments[84].

Summarizing we could group the advantages and disadvantages of BoTN in the following table:

Advantages	Disadvantages
Works whatever the cause of spasticity is	Cannot treat widespread spasticity, even for localize spasticity it is best combine with other forms of therapy
Very effective treating focal spasticity	There is a cost implication[85,86]
Adverse effects can be treated with no high complications	The effects are reversible and slowly wear off, so it has to be repeated[87]
Easy to administrate	Develop of antigenicity in the patients against the toxin[88]. Patients become "immune" to the BoTN treatment
Effective delay of surgical methods[89]	Painful and uncomfortable administration.
Repeated treatments can potentially decrease latency effect and prolonged therapeutic effect[90]	No clear and specific protocols about the specific injections sites (selection of muscles) and concentrations.

Table 6. Summarize of the BoTN treatments in patients with spasticity. Here are included children with CP, and Adults with any form of spinal cord injury and stroke.

Selective Dorsal Rhizotomy (SDR)

SDR constitutes an unselective way of reduction of cutaneous and proprioceptive awareness. The input of the afferent fibers is stopped in order to stop the motor neurons, synapsing with these afferent fibers, from firing (see Figure 4 and 5 above). Contrary to the orthopaedic surgery, SDR affects just the nervous fibers coming to the spinal cord in order to inhibit the hyperexcitability of the system. SDR is recommended for patients with scores of II and III in the GMFC scales[66]. We cannot forget that this procedure constitutes a permanent modification of the sensory-motor system at the subspinal and spinal levels, this feature of the SDR has its pros and cons; on one hand, it demonstrates an increasing benefit in terms of cost per quality adjusted life year over the time, moreover it leads to a significant reduction in soft tissue orthopaedic surgery but less impact on the need for bony surgery[91], but on the other side this permanent modification leads to a failure of the patient to be able to perform some basics skeletal muscle functions , leading to higher levels of dependency in the long term, furthermore in patients with high GMFCS scores SDR associated weakness and loss of sensitivity could lead to deterioration of some walking and standing functions[92]. Results in the literature differ in the outcome of the SDR in long term follow up analysis, stating the need of standardized post operatory procedures[93]. Although SDR does decrease the spasticity levels[94,95], several reports indicate that the effects in the muscle functionality are either not enough or absent in long term follow ups[96,97], or spasticity becomes worse after the surgery[98] or there is still need of other forms of therapy to counter long term side effects [94].

Electro-Therapy.

It is a minimally invasive method with high potential in the treatment of motor impairment pathologies first used as therapeutic treatment in 1997[99,100] although it use as a therapy strategy began in patients with motor function impairment of the upper extremity in 1979[101]. It is based in the application of electrical currents to the muscles and/or tendons in order to elicit muscle contraction or afferent fibers stimulation reactivating the spinal cord circuits and its neurons. There are several modalities depending on the length and intensity of stimulation. We will focus mainly in two out of the three modalities of Electro-Therapy (TES and NMES also mentioned in some works as TENS).

Distinctions between these modalities is worth of mention including protocols of stimulations and studies (either open or RCTs) supporting the efficacy of this methods.

Methods mentioned here are used to modify impairments and activity limitations as a consequence of spasticity in children with CP, adults with some kind of spinal cord injury and stroke. The following table describes the main three different modalities of Electro-Stimulation (ES) used in many open studies and RCTs.

Modality	Acronym	Characteristics
Functional Stimulation[102]	FES	Surface electrical stimulation to muscles and/or nerves for the porpoise of **overcoming an inability to contract** and execute functionally useful movements
Neuromuscular Stimulation[103]	NMES	Electrical stimulation to muscles **high intensity and short duration** to initiate contraction and movement
Therapeutic Stimulation[104]	TES	**Sub-threshold level stimulation** (low intensity) applied continuously for a short duration.

Table 7. Different ES modalities depending on the intensity, duration and place of application.

The specific magnitude parameters of stimulation are subject of discussion, as we will see articles and research in this field used different parameter within the same modality of stimulation, as parameters also could vary from person to person in order to elicit the desire effect avoiding discomfort , pain and skin irritations. The waveform of electrical current pulses is defined by the amplitude (mA), pulse width (µs to ms) and frequency (Hz). Often frequency and pulse width are set constant, whereas pulse amplitude varies. Stimulation parameter for successful FES are 20-50 Hz, 30-500 µs and ≤100 mA reporting no relationship between frequency and clinical outcome[105]. There are a huge number of reports and research articles in the literature supporting the use of one of these modalities in the treatment of spasticity in different UMN syndromes. We will focus in some of them pointing out the major differences and agreement between reports, as well as how these modalities have been using in different disease, especially in CP, stroke and Spinal Cord Injury (SCI). Last, all the data present in this sections comes from different review and meta-analysis performed among several hundreds of reports on ES as a therapy against spasticity, among the reviews the reader will find meta-analysis in ES in children with CP[59,106,107], Patients with Spinal Cord Injury (SCI) (http://www.bu.edu/drrk/research-syntheses/spinal-cord-injuries/spasticity)[107] and in stroke patients[107,108].

Children with CP: Kerr and colleagues (2004)[106] classified the different studies in 5 different levels of empirical research, having the level I RCT, level II non-RCT, level III Case-control study (comparison of a study with a historical control group), level IV Before and after the case and a level V or non-empirical research level (Anecdotes and/or experts opinions).

Authors	Study Design	Type of CP	Intervention	Control	Outcome measures	Results
[109]	Matched groups RCT	Hemiplegia, diplegia and quadriplegia	NMES (plus physiotherapy)	Usual physiotherapy	Gait analysis, muscle strength, ROM, GMFM, parent	ns (all measures)

					questionnaire	
110	RCT	Diplegia	TES (plus physiotherapy)	Usual physiotherapy	GMFM, seat postural control, MMT, muscle tone, ROM, PCI	GMFM (p=0.001), other measures ns
111	Matched groups RCT	Hemiplegia	NMES (plus physiotherapy)	Usual physiotherapy	ROM, MMT, gait analysis	Active and passive ROM and strength (p<0.05)
112	RCT	Diplegia	NMES (plus physiotherapy)	Physiotherapy	Radiographic measurement of kyphotic, Cobb´s and lumbrosacral angle, GMFM sitting score	Kyphonic angle, GMFM sitting score (p<0.05) other measures ns
113	Crossover RCT	Diplegia	TES (physiotherapy and stretching program)	physiotherapy and stretching program	Gait and LL function, MMt, PDMS	ns (all measures)
104	RCT	Hemiplegia, diplegia	TES (plus physiotherapy)	Placebo and usual physiotherapy	Quantitative motor-function test, ROM, Ashworth, muscle bulk	ns (all measures)

Table 8. Summarize of all level I and II empirical research performed using one type of ES in children with CP.

Authors	Type CP	Intervention	Outcome measure	Results
114	Hemiplegia	NMES	Hand function, active ROM, wrist movement	Hand function and active ROM (p<0.05)
115	Diplegia, hemiplegia	EMG-triggered NMES	Gait, UL videography, goniometry, PDMS	ns (all measures)
99	Diplegia, hemiplegia	TES (own controls)	PDMS	All test significant (p<0.01)
116	Diplegia, hemiplegia	NMES	Gait	P=0.001

Table 9. Level III and IV of empirical research studies performed on children with CP

Continuing with the review all the level V studies (n=8) reported an improvement in one of the functions and parameters studied[117-122]. We will not mention level VI studies as they are only observations with no quantifications. As we can see the effects of ES in open studies (level III and IV) are greater than those expose in the RCT (level I and II). Summing up, the results from ES as a therapy method in children with CP are very promising, although it is argued the need of increasing the number of RCT and standardized protocols[123,124].

Note: as we will see in the next chapter inervention´s method is based in level IV studies through the assessment of the mobility and spasticity level in patients before and after using Molli® for a 1 hour's session.

Cauraugh and colleagues (2010)[59] performed a meta-analysis of few selected reports divided in two different groups (n=14 for impairment and n=15 for activity limitations) with a total of 238 patients

treated with ES and 224 as control. After performing a heterogeneity test the results showed a positive effect in ES therapy improving the walking impairment and activity limitations of children with cerebral palsy (see Figure 6). Regarding to the studies included in the impairment meta-analysis several of them were performed using NMES[103,111,116,125-127] while others reports differences in the effect size using TES[103,110,113]. Regarding to the activity limitation, effectiveness several of the studies addressing walking impairment also are cited in this analysis, and here we can point out that the results were positive using any of the forms of ES available[102-104,110,126,128].

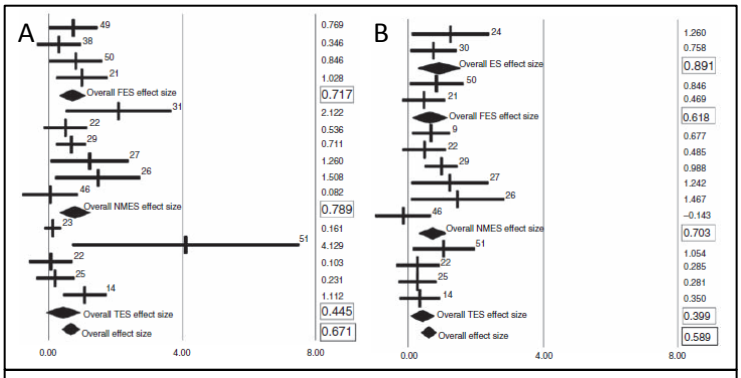


Figure 6. Forest pots showing the individual effect sizes of the 15 (A) and 14 (B) studies based on the impairment and activity limitations respectively. *Modified from Cauraugh et al., 2010*

Summarizing the results presented in ES therapy for the treatment of Cerebral Palsy, we could say that the effects of any type of ES on the spasticity level, as well as in the function improvements are generally positive. Furthermore we have pointed out here that due to these meta-analysis studies, it would be safe to assume the validity of this positive effect, as the heterogeneity or variability of the results among all these kind of studies is low, or said in other words the correlation of the effect of ES is high and reproducible among children suffering of CP.

SCI patients: Spasticity after spinal cord injury (SCI) is a common, complicated, and often frustrating impairment that is generally considered both a "health" problem[129]and a deterrent to function and quality of life[130]. The amount of reports describing effects of ES in the spasticity generated upon SCI are less compare with children with CP. Nevertheless, all the studies here review show positive results of ES treatment in spasticity level and functional recovery. Moreover some of the articles here cited attribute these therapeutically effect to the activation of reciprocal inhibition. Various methods have been employed to treat spasticity of SCI origin among them we can cite: stimulation to the antagonist muscle, application of tetanic contraction to the spastic muscle, functional electrical stimulation (FES), and transcutaneous electrical nerve stimulation (TENS), reporting beneficial effects up to 3 hours after the treatment[131-134]. The mechanism suggested for these positive effects vary among the reports, level of spasticity and muscle groups reported: Stimulation of the antagonist muscle: augmentation of reciprocal inhibition of the spastic muscle[131] Repetitive tetanic stimulation of spastic muscle: fatigue of the muscle due to repetitive tetanic stimulation[131] FES: change the mechanical properties of a spastic joint by strengthening the antagonists of the spastic muscle or might decrease the hyperactivity of spastic muscles through reciprocal inhibition[135] TENS: may involve the stimulation of large diameter afferent fibers that travel from mechanoreceptors to the spinal cord[131]. Other reports have empathized the positive effects only in the spasticity and clonus level[136,137]. Overall these reports indicated the positive effect of ES in the treatment of spasticity in SCI patients.

Stroke patients: Spasticity upon stroke is been reported to be treated using ES in all its modalities. One of the most notable reviews is done by Quandt and colleagues (2014)[108]. These authors state the obvious benefits of FES in the treatment of spasticity in stroke patient. Although this review is about

FES, which is not the electrical therapy modality exerted by Molli®, it does however bring clear and solid evidences of the benefits of the ES treatments from a numerous amount of reports. On the other hand, other reports have been published stating the benefits of other modalities of ES in stroke patients[138]. The overall results from all these studies are that either NMES or FENS are valid and solid therapies to treat spasticity in stroke patients[107,139-143]. However as we will see in the next chapter, one of the most exciting observations coming out of the application of ES in stroke patients is the possibility that this therapy may affect processes of neuroplasticity, helping the CNS to keep the uninjured cells and support the compensation mechanism exerted by other brain areas upon damage after a ischemic episode in the brain.

Inerventions´ Protocol

The data regarding therapeutically effects of the ES in the treatment of spasticity associated with CP, stroke and SCI is irrefutable. Nevertheless, a reduction in spasticity is also seen in all possible treatments here described. The question remains in the effects of these treatments in the function of the muscles and the increase of the Quality of Life after the treatments are initiated. One of the main advantages of the ES therapy over the rest of therapeutic modalities is that there is not blockage or loss of function when the muscle or nerves are electrically stimulated, in other words, the electrical stimulation uses the neurons and spinal circuits already presented in the body to improve the function of the muscles and reduce the spasticity. This also offers another exciting and intriguing possibility as a side effect of the ES: neuroplasticity.

In this chapter we are going to focus in two exclusive features presented in the ES therapy compared to any other treatment available for patients presenting spasticity as an outcome of the UMNS: the reciprocal inhibition and neuroplasticity in the spinal and cortical circuits elicited by the activation of the peripheral and spinal circuits.

Reciprocal inhibition: It has been described as a plausible mechanism of reduction of spasticity based on the inactivation of the antagonist (spastic) muscle through activation of the agonist muscle[144-146]. The idea of reciprocal inhibition as the cause behind the ES came from previous reports describing improve of gait and other muscle function after training, leading to the hypothesis that sensory feedback is a critical factor for training spinal locomotor networks[147,148], moreover reciprocal Ia afferents inhibition has been showed in dynamic modulation during voluntary movements[149,150]. Taking all this into account there are proven evidences of the fact that activation of the existing neuronal circuits upon an insult or damage can help in the recovery and improvement of locomotion faculties. *ES therapy is based in "training" of the spinal cord network.* As physical training helps in rehabilitation, electrical stimulation of these same neuronal circuits results in an efficient training of the synapsis and neuronal functions at spinal and sub-spinal levels.

As we showed in the first part of this document, this neuronal activity at spinal levels could also affect higher levels of the motor system, as it is not an isolated system, but it sends signals to the motor and sensory cortex, it is plausible to think of the possibility of an effect at the brain level and the ascending and descending tracts communication the brain and the spinal cord.

Neuroplasticity: ES stimulation constitutes a "neural training" therapy, unlike all other forms of therapy, ES does not inhibit the neuronal signal at any level as the baclofen (inhibition of all neurons in the spinal cord) or botulinum toxins (inhibition of the Ach release to the muscle and therefore stopping the contraction signal) or stops the signal sending process as the SDR. Thus, ES works in a completely different fashion as other therapies facilitating the synapses of all neurons involved in the spinal circuits (see figure 7). This neuronal activation helps the neurons to keep their synapses and all elements involved in the synaptic transmission active and working, furthermore this activity sends signals to the cortex where plasticity has been shown as a result of the motor-sensory feedback from the muscles and spinal cord[151-153], moreover this "neural training" is been hypothesized as a responsible of a possible plasticity at spinal levels increasing the feedback signals sent to the higher nervous system structures[154].

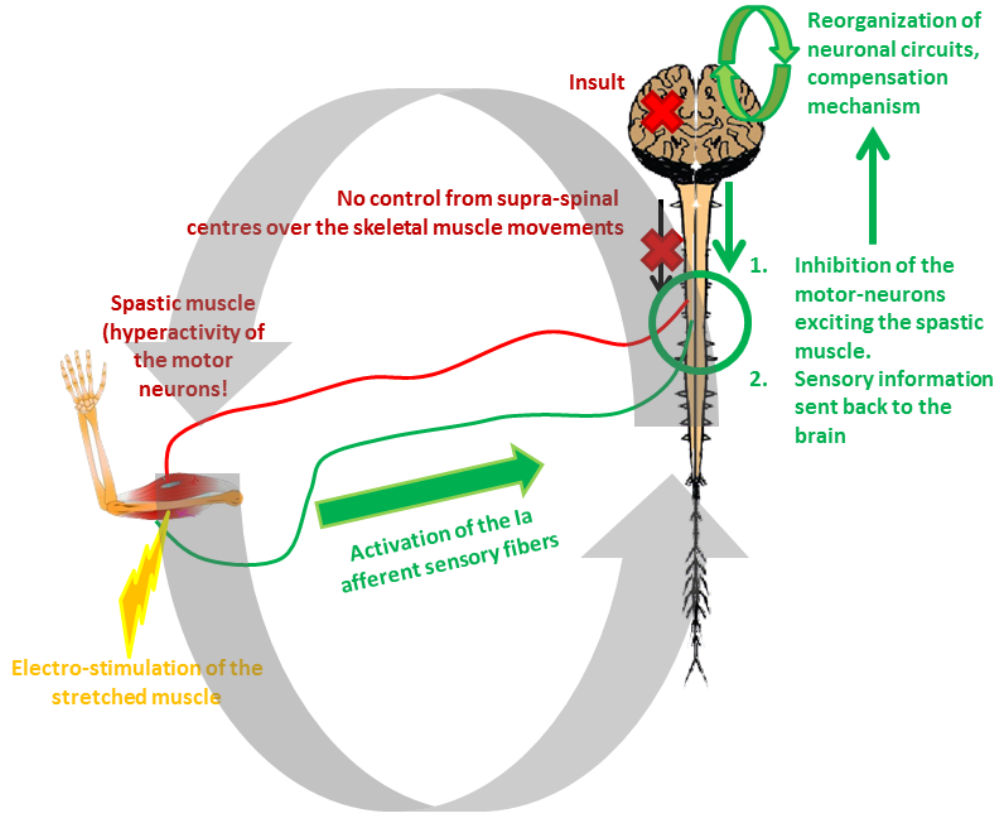


Figure 7. Feedback mechanism exerted by intervention´s method. Evidence from basic science, however, demonstrates that the central nervous system after injury is malleable and can learn. After an insult or injury in the upper motor centres, the control of the reflex movement is heavily impaired, resulting in spasticity (red arrows and text). Using ES in the muscles signals are sent to the spinal cord and the brain helping in this activity-dependent neuroplasticity, supporting the idea of a compensation model, where the upper motor centres could remodel their connections and affect the control of the reflexes thanks to the information sent by the reflex mechanism, closing in this way the circle of plasticity

Summary

The inervention´s method is based in the application of electrical stimuli onto the muscles in order to facilitate the process of reciprocal inhibition exerted naturally by the central nervous system at the spinal cord level. As we have discussed before ES is a non-invasive, feasible and relatively cheap effective method that helps the body to "train neuronal circuits" in order to reduce spasticity. Summarizing all articles and research reports here presented, there is no an infallible method, but these methods should be considered depending on the type of disease, outcome, type of patient, degree of the symptoms and severity. All other methods here mentioned have also been proven to help in spasticity and most notably as many authors have claimed a therapy approach based in the combination of two or even three of these methods, that could add an additive effect and better and faster positive outcomes in the spasticity´s therapy. Nevertheless ES is the only method available to date that promoters training at different levels (muscle contraction, neuronal synapsis, information transmission…) and makes possible…..

….to use the body´s resources as a tool against the spasticity"

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