PAIRED ASSOCIATIVE STIMULATION FOR SPINAL CORD INJURY REHABILITATION: A CASE STUDY

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ABSTRACT

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The purpose of this study was to replicate a paired associative stimulation (PAS) therapeutic intervention to improve the motor output in one tetraplegic individual's hands. PAS is a paired brain and nerve stimulation method using transcranial magnetic stimulation (TMS) and peripheral nerve stimulation (PNS). Tetraplegia is a neurological injury to the spinal cord which hinders voluntary movement of upper and lower limbs, with varying degrees based on the level of the spinal cord which is severed. Utilizing a PAS protocol aims to target the neuroplasticity in the CST to improve motor function.

The intervention was given for 6 weeks, with a total of 22 individual sessions. This intervention tested the clinical feasibility of a high PAS protocol, as it used slightly altered stimulation conditions compared to the original protocol. Physiotherapy assessments were conducted pre-, post-, and 1-month post-intervention. This was the main evaluation method to assess functional motor improvement in the hands. Average motor evoked potentials (MEPs) recordings were also measured using TMS at pre- and post-intervention.

After 6 weeks of PAS therapy, functional motor output increased in both hands, which had been diminished due to the injury. In the left hand, all the stimulated muscles saw improvement in the functional measures (physiotherapy assessments). In the right hand, only two of the three stimulated muscles saw minor improvements (extensor digitorum and abductor pollicis brevis), due to the lack of visible MEPs, measured by the TMS, in the abductor pollicis brevis and the abductor digiti minimi.

To conclude, the original PAS protocol was successfully modified to yield positive results. Further studies should be conducted in the future for a longer duration to validate the clinical feasibility.

Keywords: transcranial magnetic stimulation, paired associative stimulation, spinal cord injury, neuroplasticity

ABBREVIATIONS

AIS	ASIA Impairment Scale
APB	Abductor Pollicis Brevis
ASIA	American Spinal Injury Association
CNS	Central Nervous System
CST	Corticospinal Tract
EMG	Electromyography
ISI	Interstimulus Interval
LTD	Long-Term Depression
LTP	Long-Term Potentiation
MEP	Motor Evoked Potential
MNI	Montreal Neurological Institute
MSO	Maximum Stimulator Output
M1	Primary Motor Cortex
M11	Secondary Motor Area
NLI	Neurological Level of Injury
NMDA	N-methyl-D-aspartate
nTMS	Navigated Transcranial Magnetic Stimulation
PAS	Paired Associative Stimulation
PNS	Peripheral Nervous System
rMT	Resting Motor Threshold
rTMS	Repetitive Transcranial Magnetic Stimulation
SC	Spinal Cord
SCI	Spinal Cord Injury
sEMG	Surface Electromyography
STDP	Spike-Time Dependent Plasticity
TES	Transcranial Electrical Stimulation
TMS	Transcranial Magnetic Stimulation

CONTENTS

1 INTRODUCTION

Paired associative stimulation (PAS) is a non-invasive stimulation approach aimed to improve synaptic plasticity. Synaptic plasticity is referred as the ability of neuronal connections to make changes by strengthening or weakening connections, on a temporary or permanent basis. Synaptic plasticity can occur at multiple levels, including the cortex, corticospinal tract, and spinal cord. Both invasive and non-invasive approaches have been developed to facilitate plasticity in the human motor system. (Purves et al. 2019, 169-171) One non-invasive approach pairs transcranial magnetic stimulation (TMS) with peripheral nerve stimulation (PNS) to facilitate long term plastic changes. PAS relies on the timing of descending (TMS) and ascending (PNS) volleys. This timing determines whether the plastic changes strengthen or weaken the synapses (Jo et al. 2020).

Several approaches exist to elicit changes in neuronal connections and communication for spinal cord injury (SCI) to improve motor function. SCI is a traumatic neurological injury to the human nervous system, disconnecting communication between the brain, spinal cord, and periphery (Brown & Martinez 2019). The present study aims to facilitate spinal cord plasticity in 1 chronic tetraplegic individual, to improve their hand function utilizing a high intensity, high frequency PAS protocol. It is a 6-week intervention targeting muscles abductor pollicis brevis, extensor digitorum, abductor digiti minimi. The aim is to generate the strengthening of synaptic connections in the altered corticospinal tract to facilitate positive motor function in the targeted muscles.

2 LITERATURE REVIEW

The literature review aims to explain neural control of movement and non-invasive methods for mapping and rehabilitating altered nervous systems. It follows a bottom-up approach starting with basic nervous system operation, followed by neural plasticity and injury, and ending with complex modern methods of neural imaging and stimulation.

2.1 The Human Nervous System

The human nervous system, made up of billions of neurons, is the primary communication system for the body. This network of nerve cells has two major divisions: the central and peripheral systems. The periphery sends information, via sensory receptors, to the central nervous system (CNS). The CNS determines the appropriate motor response to return to the motor system. (Longstaff & Ronczkowski 2011) This happens because of interneural connections. Electrical signals travel down the axon and the axon hillock of the neuron, transferring the signal from one axon terminal to the dendrites, the soma, as well as other axons of another neuron. This transfer of electrical signal happens at the synapse (chemical or electrical). The chemical synapse requires neurotransmitters. At the neuromuscular junction, a spinal motor neuron synapses with a skeletal muscle cell. When it reaches the action potential threshold, the neuron depolarizes the muscular membrane. Afferent neurons are sensory neurons that receive peripheral information based on a physiological stimulus. Efferent neurons are motor neurons (in the motor pathway) that can project to other regions of the nervous system via interneurons or directly onto a muscle. (Purves et al. 2019, 10)

2.1.1 Central Nervous System

The CNS consists of the brain and spinal cord. Within the brain, the CNS includes the cerebellum, medulla, pons, midbrain, diencephalon, and telencephalon. The cortex covers the cerebrum (part of the telencephalon) and the cerebellum. The cerebral cortex is involved with most brain activity, including planning and executing voluntary movement, cognitive function, and sensory perception. (Longstaff & Ronczkowski 2011) The spinal cord (SC) extends from the base of the skull to the lumbar region vertebrae. The SC receives from the sensory neurons in the periphery via muscles, skin, and joints. It also houses the motor neurons that project to

the skeletal muscle. These neurons travel through the grey matter of the SC, with motor neurons travelling through the ventral horns and sensory neurons travelling through the dorsal horns. The white matter of the SC is the pathway for ascending and descending neural tracts to and from the brain (sensory information to the brain, motor commands from the brain). (Longstaff & Ronczkowski 2011)

2.1.2 Peripheral Nervous System

The peripheral nervous system (PNS) is responsible for routing nerve signals to and from the CNS. The PNS is subdivided into somatic and autonomic components. The fibers in each division and subdivisions have unique properties to serve their role (Paggi et al. 2021). The somatic system receives sensory information via sensory receptors on skin, muscles and joints about mechanical forces, pain, and temperature changes (mechanoreceptors, nociceptors, and thermoreceptors). This information travels to the CNS, where it is interpreted and returned as an appropriate response through the periphery to efferent motor neuron axons for a skeletal muscle response. Within this category, for example, the afferents transferring information about mechanical forces are large and myelinated, which increases saltatory conduction, thus increasing the conduction velocity of action potentials (Paggi et al. 2021). The autonomic nervous system is the regulatory system for smooth muscle, viscera, and glands. The autonomic nervous system is divided into sympathetic, parasympathetic, and enteric systems. Sympathetic is the fight or flight response to stressors, parasympathetic maintains homeostasis, and the enteric system maintains gastric smooth muscle. (Amaral 2000, 335)

2.2 Neural Control of Movement: From Brain to Muscle

The brain is responsible for initiating voluntary movement. Thus, this section follows a top-down approach from brain to muscle. The cortical area, specifically the motor cortex, is the most studied and agreed upon location that initiates voluntary movement (Purves et al. 2019, 358). The spinal cord also has a governing over posture and locomotion, thanks to a mechanism of central pattern generators that provide cyclic phase dependent information. Finally, the muscular system must interpret all this information and perform the movement.

2.2.1 Motor Cortex

The motor cortex–a part of the cerebral cortex–is the primary cortical motor area which coordinates voluntary movement. The motor cortex can be divided into the primary motor cortex (M1), premotor area and supplementary motor area (M11). Other neural structures – such as the basal ganglia, cerebellum, brainstem centers, and local circuit neurons–contribute to the control and execution of movement. (Purves et al. 2019, 355-381)

The corticomotoneuronal system starts with the pyramidal cells in layer V of the cortex, primarily from M1 and M11 (Longstaff & Ronczkowski 2011). It consists of the descending corticospinal tract (CST) axons and their monosynaptic projection onto spinal alpha-motor neurons. The CST is thought to be the main contributor to voluntary expression of precise, skilled movement of distal limb areas (Purves et al. 2019, 382). For voluntary planned movement, the upper motor neurons of the cortex integrate excitatory and inhibitory signals, translating it into a signal to initiate or inhibit voluntary movement (FIGURE 1). These upper motor neurons facilitate the discharge of functionally linked neuron groups for precise movement. The action potential travels down from the cortex, through the white matter of the brainstem, reaching the medulla. Here at the pyramidal decussation, approximately 90% of the neurons cross over and continue down to the SC. (Purves et al. 2019, 384)

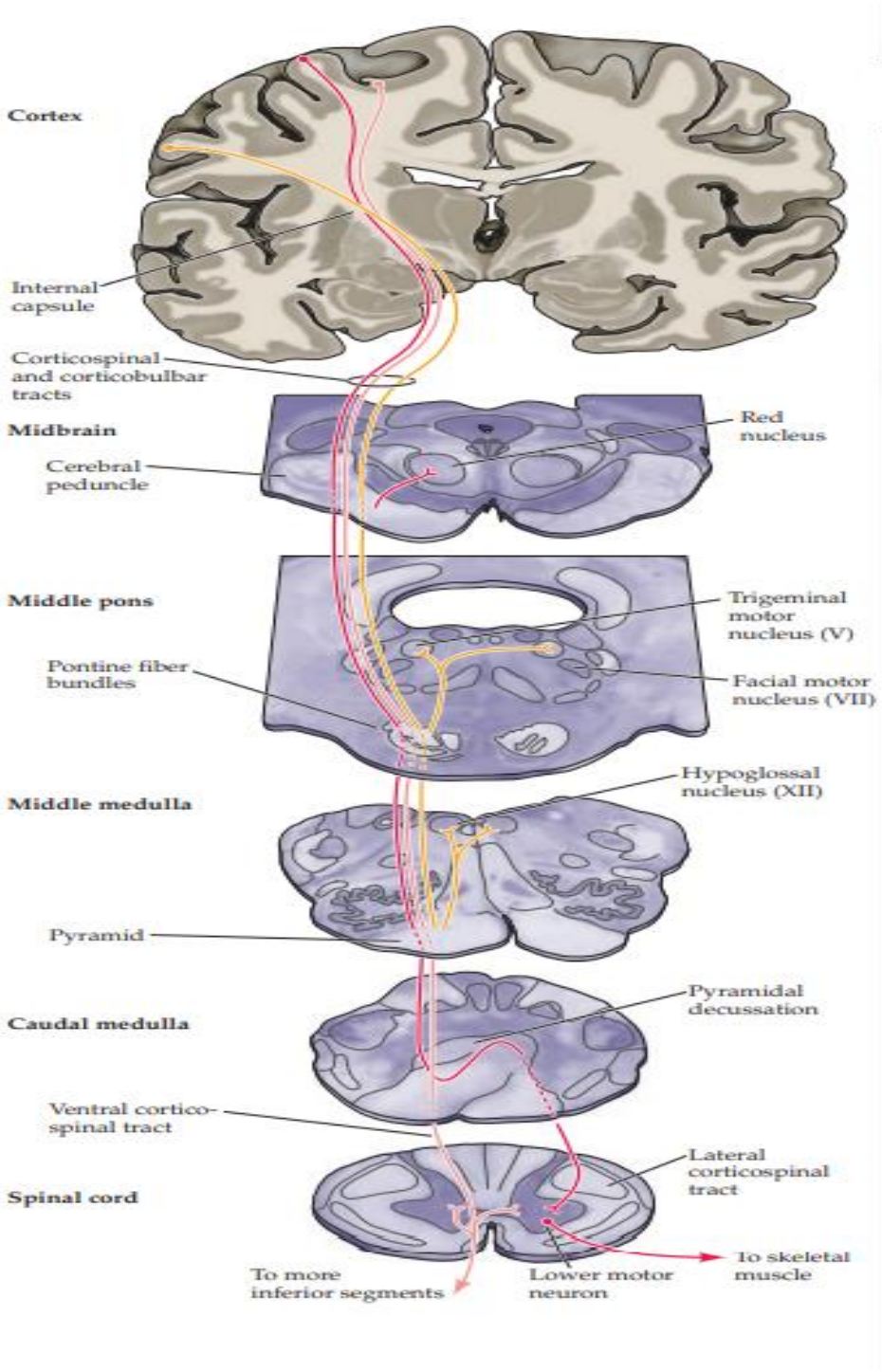

FIGURE 1: The descending path of the CST, from the cortex, through the brainstem to the SC (Purves et al. 2019, 384).

Motor maps, known as Brodmann's areas, provide classification of cortical areas based on their cytoarchitecture (Brodmann 2006/1909). These areas have been referenced for over a century and led to the creation of the motor and somatosensory homunculus. The somatosensory and motor homunculus represents a spatial map of the brain areas associated with the contralateral

motor and sensory output throughout the body (Penfield & Boldrey 1937). The motor homunculus resides in Brodmann's area 4, and the somatosensory homunculus in Brodmann's area 1-3. The motor map can be evaluated via electrical stimulation, as well as non-invasive brain stimulation, for example TMS. The movement response to excitation is assessed based on the targeted movement along the homunculus (FIGURE 2). It does not identify individual muscle contractions. For example, a stimulus to one point can activate multiple muscles, just as a single muscle can be activated by multiple stimulation points (Peterson et al. 2002).

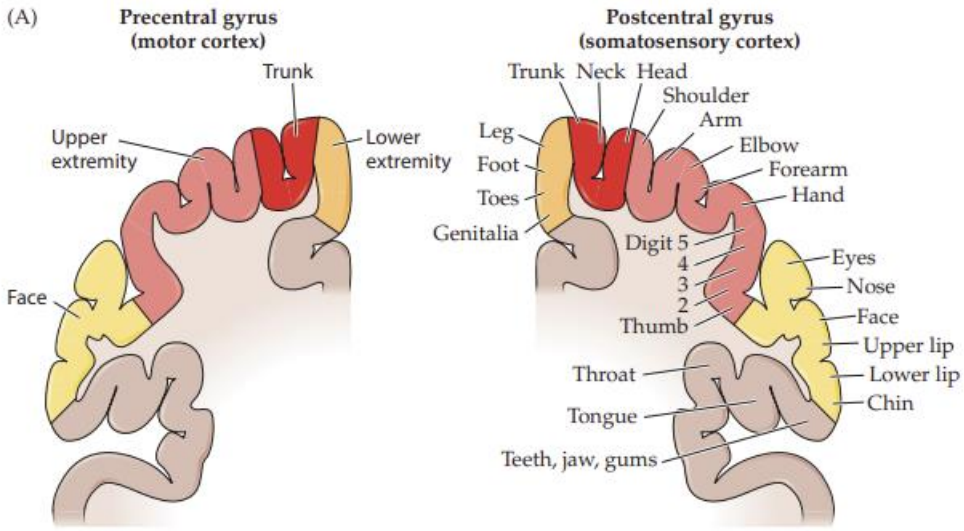

FIGURE 2: Motor (precentral gyrus) and somatosensory (postcentral gyrus) homunculus, representing a spatial map of the contralateral motor/sensory output.

2.2.2 Spinal Cord

After the pyramidal decussation, the upper motor neurons continue down the lateral CST of the SC until reaching the desired ventral root exit point. Here, the upper motor neurons will synapse directly to the spinal motor neurons in the grey matter at the cortico-motoneuronal synapse. For example, the motor neuron pools innervating the arm reside in the cervical enlargement of the SC. The motor neuron pool for a muscle consists of all the lower motor neurons that innervate the muscle fibers of a single muscle. (Zayia & Tadi 2022)

The lower motor neurons transfer the excitatory or inhibitory signal to the effector muscle. The main type of lower motor neuron responsible for skeletal muscle contraction is the somatic

motor neurons, with alpha and gamma types. Alpha motor neurons are larger motor neurons that directly connect to the skeletal muscle for contractile force. Gamma motor neurons are smaller motor neurons that innervate intrafusal muscle fibers (muscle spindles) to regulate sensory input about the length of the muscle. Together, the lower motor neuron types optimize coordinated movement. Thus, lower motor neurons are the final common pathway for information from descending and sensory input to the skeletal muscle. (Purves et al. 2019, 357)

2.2.3 Muscle Structure

Muscle tissue is the only tissue capable of creating movement, due to its elastic, contractile, extensible, and elastic properties. The three categories include skeletal, cardiac, and smooth muscle (Enoka 2008, 205). Skeletal muscle is responsible for producing voluntary movement of the skin and skeleton. When an excited lower motor neuron reaches the skeletal muscle at the neuromuscular junction, it releases a chemical signal via neurotransmitter (acetylcholine). This neurotransmitter binds to the receptors of the muscle fiber, starting the chemical reaction in the muscle to produce the contraction. Each skeletal muscle is innervated by a somatic motor neuron, and one motor neuron innervates many muscle fibers (the motor unit). (Enoka 2008, 178-190)

2.3 Plasticity

Plasticity is the adaptive/maladaptive changes that occur in neural networks in response to lifespan development, training, or injury. Synaptic plasticity pertains to changes in the synaptic connections between neurons. These changes to synaptic transmission occur due to the complexity of their connectivity, which is modulated persistently by neural activity. Plasticity can express a multitude of adaptations to synaptic transmission, based on persistence of the modulatory input (short or long term) as well the input target on the synaptic connection. These changes can present positive or negative effects to the functionality of synaptic communication. Not only can plasticity occur in different areas of the synaptic connections, but along different areas of the central nervous system. This includes cortical regions, as well as regions of the corticospinal tract. (Purves et al. 2019, 169-173)

2.3.1 Short- and Long-Term Synaptic Plasticity

Synaptic plasticity can either have a short- or long-term effect. Short-term changes include effects of facilitation, depression, augmentation, and potentiation. In terms of neurorehabilitation, long-term plasticity could be favored to establish chronic positive change in a negatively altered nervous system. However, short-term plasticity is also investigated for neurorehabilitation. Once example can be seen in methods of "priming the brain" for rehabilitation sessions. In this case, short-term plasticity methods are used to facilitate long-term alterations (Schabrun & Chipchase 2012). For the rehabilitation to be utilizing long-term plasticity methods, the activation requires correlation of the presynaptic and postsynaptic neurons (Ling et al. 2020). Long term changes include long-term potentiation (LTP) and long-term depression (LTD). These long-lasting synaptic changes permanently modify brain function. LTP and LTD like plasticity is time dependent on pre and postsynaptic neuron activity. Based on Hebb's postulate, LTP and LTD require coordinated activity of the presynaptic terminal and postsynaptic neuron to alter the synaptic connection (Purves et al. 2019, 176-178). This synchronized or paired synaptic activity is phrased "neurons that fire together, wire together" (Hebb 2005). LTP would strengthen the connection, whereas LTD would weaken the connection. It is important to understand when considering altering the plasticity of the nervous system, at any level, can have adaptive or maladaptive effects, depending on the neurological condition of the individual.

2.3.2 Corticospinal Tract Plasticity

Animal lesion experiments, as well as a few documented human cases, suggest that a multitude of voluntary movements can occur with a severed CST (Petersen et al. 2003). Simultaneously, there is documentation of voluntary movements occurring with only the CST intact. For example, one study found that a single patient with a tumor invading all the brainstem except the pyramidal tract maintained voluntary movements (Peterson et al. 2003). In either condition, it shows adaptability with and without CST. Thus, plasticity occurs within the human motor system and the CST is capable of compensating for neurological dysfunctions. However, this does not directly indicate the CST is the only tract responsible for voluntary movement in normal conditions.

2.3.3 Spinal Cord Plasticity

The spinal cord and cortical areas rely on each other for functional movement. Logically, if the cortical area has plasticity, then the connecting spinal cord should be adaptable as well. Evidence exists proving that the spinal cord has plasticity. One example is in a study using the method of decerebrating cats to induce a partial spinal cord injury (affecting just one limb) in the thoracic region (Gossard 2015). They assessed the plasticity of the central pattern generator within the spinal cord, which provides the ability for cyclic movements such as locomotion. By stimulating the sciatic nerve to both limbs to trigger fictive locomotion, they found that the right limb, which was cerebrated, had drastically depressed central pattern generator activity. The main finding was that central pattern generator circuitry is susceptible to spontaneous plasticity, in addition to the sensory activation and supraspinal inputs to the spinal cord. (Gossard 2015)

2.4 Nervous System Injury

The previously described “normal” scheme of motor control in the body can be altered due to neurological injury. Neurological injury is an injury to the brain, spinal, and or nerves. There are many conditions in which the nervous system is altered, but the focus of this review pertains to spinal cord injuries. A spinal cord injury (SCI) is a debilitating neurological injury that leads to loss or reduced motor, sensory and autonomic function (Brown & Martinez 2019). Causes of injury can be due to traumatic incident, disease, or degeneration of spinal nerves. A traumatic injury is a result of compression, transection, contusion, or shearing forces applied to the spinal cord (Hachem et al. 2021). This initial traumatic injury is followed by three phases of secondary injury: 1. Acute (first 48 hours)/inflammatory response 2. Subacute (up to 2 weeks)/maturation of injury site 3. Chronic. Once the individual is in the chronic stage, there is remodeling of sparred circuits and regeneration of neural networks that may be advantageous or disadvantageous plasticity (Hachem et al. 2021). This dramatic loss of neurons in the SC at the point of lesion leads to various levels of reduced motor, sensory, and autonomic function, below the level of lesion. This point of lesion is considered the neurological level of injury (NLI).

Based on a recent epidemiology review of SCI incidence in Finland, they found that the mean annual incidence of a traumatic SCI was 36.6 per million, with an annual number of 200 new

cases per year (Johansson et al. 2021). Compared to a global review of Western Europe incidence of 16 per million person per year, Finland has a greater rate of incidence. Thus, rehabilitative and preventative strategies are a vital area of research.

2.5 Transcranial Magnetic Stimulation

TMS is a non-invasive brain method of cortical areas. TMS sends a magnetic field to the brain, generated by a coil outside of the brain (FIGURE 3). According to Faraday's law, this magnetic field elicits an electrical field in the brain. This electrical field activates the cortex, depolarizing the cell membranes of layer V pyramidal neurons. This generates an action potential of the upper motor neuron, propagating down SC and synapsing onto the lower motor neuron to activate the target muscle. (Petersen et al, 2003; Rossini et al. 2015) The target muscle is a representation of the stimulated motor cortex area (Laakso et al. 2014).

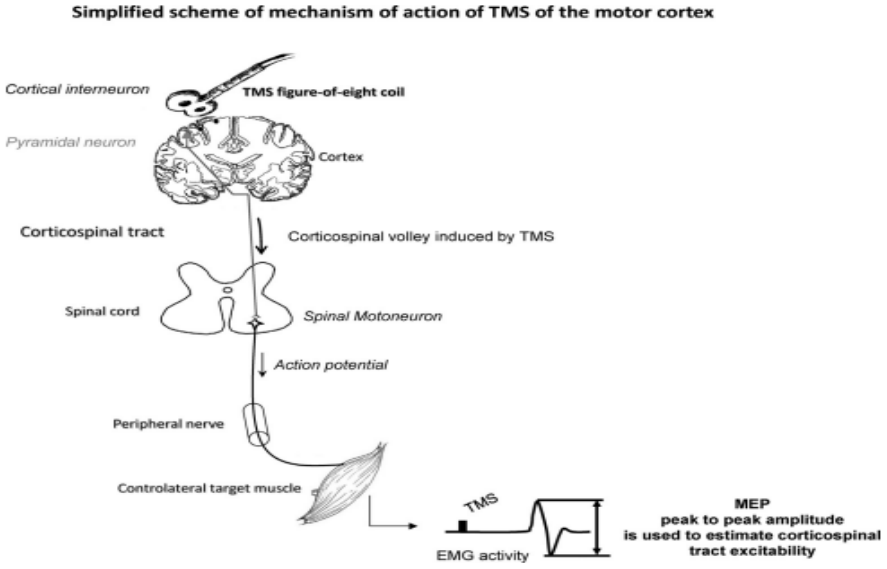

FIGURE 3: TMS activation of the motor cortex. Flat figure-of-eight coil stimulates an area of the motor cortex, an action potential travels down the CST to spinal motor neurons, creating a motor response in the contralateral muscle. The muscle response is expressed as a MEP (Klomjac et al. 2015).

2.5.1 Motor Evoked Potential

A motor evoked potential (MEP) is the functional response to TMS. MEP amplitudes indicate the location of dominant neuronal populations for a target muscle (Kallioniemi et al. 2015). MEP amplitude relies on two things: the excitation of the corticospinal cells and the spinal motor neurons (Peterson et al. 2003). Thus, MEP is considered an indicator of excitability in the corticospinal tract. MEPs are visualized using surface electromyography (sEMG). sEMG is a non-invasive imaging technique used to evaluate and record the electrical activity of the skeletal muscle (Raez et al. 2006). Two electrodes in bipolar arrangement are placed on the surface of the skin, parallel to the muscle fiber direction at the most prominent portion of the muscle belly. sEMG generates a waveform-like image that demonstrates information about electrical muscle activity (Raez et al. 2006).

MEP latency is an expression of the corticomotor conduction time. Compared to MEP amplitude, latency can indicate which pathways have the most direct connections, in other words the shortest latency (Kallioniemi et al. 2015). MEP latency can be used to find the central motor conduction time, which is the time it takes the signal to travel from the cortex to the motor neuron pool in the spinal cord. This requires a calculation of peripheral conduction time (Hallett 2007).

In transcranial electrical stimulation (TES), a brief, high intensity electric shock is delivered through the scalp over the M1. This is done by placing electrodes on the scalp. Since TES stimulates the brain directly, it produces a shorter MEP latency than TMS. TMS, unlike TES, typically does not produce a D-wave, which is a direct activation of descending axons. TMS generally produces I-waves, which is indirect activation of the descending axons via transsynaptic activity (Laakso et al. 2014). This indirect activation means that previously mentioned pyramidal cells can also affect motor responses observed with TMS.

2.5.2 Hotspots and Motor Thresholds

To identify the motor area for a target muscle on an individual's brain, one must "map" the cortex. This involves stimulating the reference area on the motor homunculus (each brain is unique) until the hotspot is identified. The hotspot is the cortex area that elicits the greatest MEP amplitude and the proper motor response. The motor threshold can then be taken at the

hotspot. Active and Passive Motor Threshold describe the lower limits of TMS intensity required to evoke the MEP response in the target muscle in the active and passive condition, respectively. (Kropotov 2016) It is a reference value to assess neuromuscular dysfunction, set stimulation parameters, and track progress in a rehabilitation program (Hallet 2007). Motor imagery decreases resting motor threshold (rMT); especially important in neurological patients as MEPs can be difficult to achieve at reasonable stimulation intensities. Decreasing the motor threshold also allows you to stimulate at lower intensities, which is required for some TMS testing methods (ramp protocols) (Sutbeyaz et al. 2007).

2.5.3 TMS Considerations

Coil type, coil orientation, stimulation intensity, and waveform affect TMS outcomes. TMS coils can differ in shape and size, which alters the electric field strength, depth and focality of stimulation. For example, a database compared electric field strength of 25 commercially available TMS coils of different arrangements. It found great differences between coils in electrical field strength as well as depth and focality tradeoff (Drakaki et al. 2022). The intensity of stimulation in any coil type determines the spatial spread of the current. A higher stimulation intensity will activate a wider spread of neurons in the cortex. Additionally, the higher stimulation intensities are required to target the lower extremity compared to lower stimulation intensities for the upper extremity (Groppa et al. 2012).

Coil orientation also affects electric field strength and depth of penetration. Computational investigations of optimal coil orientations have shown that the cortex is most sensitive to electric fields that are perpendicular to the cortical layers (Laakso et al. 2014). Thus, it is recommended to start hotspot mapping with the coil position parallel to the individual´s head and anteromedial to the midline. From this reference point, you can alter the lateral, vertical, and longitudinal positioning of the coil to strengthen the efficacy of the electrical field. The largest MEP results typically occur with an anterior-posterior coil angle orientation (Hallet 2007).

TMS can have “monophasic” or “biphasic” waveforms. Monophasic has a strong initial current flow, while biphasic has a cosine waveform orientation (Groppa et al. 2012). With monophasic waveforms, only the first initial phase of the stimulus is strong enough to elicit action potentials.

In the biphasic waveform, the second, reversal phase is the strongest. The biphasic waveform is more commonly used in repetitive TMS (rTMS) protocols (Rossini et al. 2015)

2.5.4 Navigated TMS

Neuronavigated TMS (nTMS) has become a tool to improve intersession repeatability and intrasession accuracy. Neuronavigation systems tract coil location via a targeting system, based on the anatomical position on the head in real time. A magnetic resonance imaging (MRI) file or a Montreal Neurological Institute (MNI) generated brain image is used to achieve the landmark guided TMS mapping (Sondergaard et al. 2021). This navigated approach to TMS creates specific scalp landmark coordinates based on the underlying cortical features, making it more reliable for cortical mapping and improving the repeatability of accurate simulations between sessions (Sondergaard et al. 2021).

2.6 Peripheral Nerve Stimulation

Peripheral nerve stimulation is a type of electrical stimulation targeting a peripheral nerve or a series of peripheral nerves (Paggi et al. 2021). When a peripheral nerve is electrically stimulated, it is recorded as a compound muscle activation potential (CMAP) with a sEMG signal on the targeted nerve-muscle pairing (Groppa et al. 2012). Peripheral nerve stimulation can be used to identify the activity of motor and sensory neurons. These can be seen with different waveforms, for example M-wave, F-wave, and H-wave (FIGURE 4).

M-wave stimulation targets the alpha motor neurons by gradually increasing electrical stimulation intensity. It is a representation of the motor response. As you gradually increase the intensity of stimulation, the group 1a afferents excitation will slowly decrease as alpha motor neuron excitation increases. It should appear at approximately 5-10ms of latency. (Kai, S. & Nakabayashi, K. 2013) As you increase in intensity, the M-wave will continue to grow. This is because with the increasing intensity, the antidromic volley (towards the spinal cord) gets larger, thus overpowering the response of the orthodromic volley (towards the muscle) (Palmieri et al. 2004).

The F-wave is a representation of antidromic activation of motor neurons by strong electrical stimulation of peripheral nerves (Peterson et al. 2003). F-wave travels through the motor axon antidromically and back to the muscle. The F-wave serves as an indicator of peripheral motor conduction. The late latency F response depends on the stimulation site (longer in the lower limbs) and age (Peterson et al. 2003). The F-wave has some similarities to the H-reflex but differs in a few ways.

H-reflex, also known as the stretch reflex, is a representation of monosynaptic reflex of the 1a afferents, as the lower intensity travels first the 1a afferent, and then to the motor axon (Palmieri et al. 2004). With the F-wave, because you stimulate at a higher intensity, it overcomes the reflex. For example, the F wave starts at a supramaximal stimulation intensity, whereas the H-reflex gradually disappears when stimulation intensity is too high. This is why there is a decrease after the reflex has already plateaued. This disappearance is due to the antidromic collisions overpowering the action potentials of the orthodromic activity (Palmieri et a. 2004).

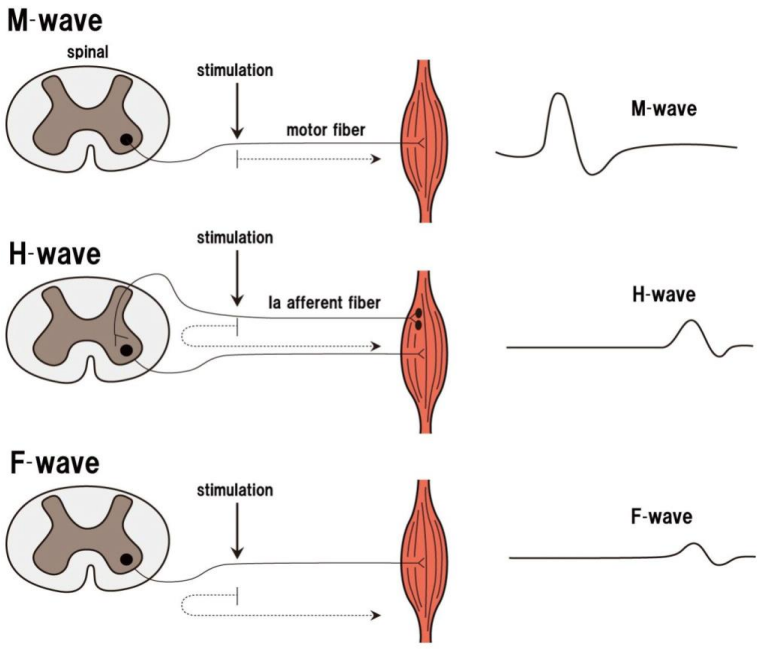

FIGURE 4: M-wave: stimulation to the efferent. H-wave: stimulation via monosynaptic reflex. F-wave: stimulation in the antidromic direction. (Kai, S. & Nakabayashi, K. 2013)

2.7 Paired Associative Stimulation

PAS is a combined noninvasive paired stimulation method, utilizing descending and ascending neural pathways within the corticospinal tract (Ling et al. 2020). The use of TMS and PNS has been shown to generate corticospinal excitability through spike-timing-dependent plasticity (STDP). The Hebbian postulate can explain how neural circuits develop. Synaptic terminals strengthen via correlated activity throughout human development stages. PAS utilizes the effect of LTP (long term synaptic plasticity) to strengthen synaptic connections through coordinated orthodromic and antidromic activity. The timed pre- and post-synaptic connections release neurotrophins to facilitate structural changes in the synaptic connections. Spinal PAS targets the corticomotoneuronal synapses of the cervical spinal cord for structural reorganization via neurotrophins released. PAS can combine brain stimulation with either spinal cord stimulation or peripheral nerve stimulation (Ling et al. 2020), as well as target either cortical or spinal areas of the corticospinal tract. (Tolmacheva et al. 2017).

Conventional PAS protocols rely on precise interstimulus intervals (ISI). ISI refers to the timing of the TMS and PNS pulses. The time at which the volleys collide determines both the location of the effect (cortical or spinal), as well as the facilitation or depression of corticospinal excitability (Jo et al. 2020). The descending pulse should arrive at the preferred site before the ascending pulse to facilitate LTP, according to STDP. ISI intervals are typically determined based on an equation F-response (F-wave) latencies or maximum M-wave, MEP values, or target muscle evoked potentials (Ling et al. 2020). These equations are determined based on the values that can be derived from the participants and the conditions of the PAS protocol.

2.7.1 Mechanisms of Paired Associative Stimulation

One component of PAS often discussed is spike timing dependent plasticity (STDP), the temporal order of pre and postsynaptic spiking (Jo et al. 2020). The spike timing of descending and ascending inputs at the stimulation site on the CST determines whether an excitatory or inhibitory effect occurs in the targeted area. LTP appears to occur when the orthodromic volley arrives before the antidromic volley. LTD appears to occur when the antidromic volley arrives before the orthodromic volley (Ling et al. 2020). These “orthodromic” and “antidromic” volleys are terms used to describe the signals sent through the corticospinal tract when TMS and PNS

create electrical activation. They can also be referred to as “descending” and “ascending”, respectfully. The mechanism behind STDP isn’t clear, but it is thought to involve N-methyl-D-aspartate (NMDA)-type glutamate receptors and the influx of Ca^{2+}. There is speculation on how the Ca^{2+} influx determines the LTP/LTD effect (amplitude, rate of flow, location of Ca^{2+}). However, Ca^{2+} appears to be the main contributing factor, and the timed arrival of the orthodromic and antidromic volleys affects this Ca^{2+} activity (Jo et al. 2020).

There are additional factors to facilitate an LTP effect besides STDP, or means of overcoming the precision required to utilize STDP. One way is to increase the total number of volleys colliding with each other to increase the likelihood of LTP. This could be done by increasing the intensity of the TMS, which in turn increases the number of descending volleys to collide with the ascending volleys. By increasing the number of collisions, with LTP-inducing and LTD-inducing simultaneous collisions, the LTP can overpower the LTD (Sjöström et al. 2001). Additionally, the frequency of the peripheral component can be increased to provide the same effect (Tolmacheva et al. 2019). Combining a high intensity TMS stimulation and a high frequency peripheral component can diminish the need to have precise interstimulus intervals (Shulga et al., 2016).

2.7.2 Paired Associative Stimulation for Spinal Cord Injury Motor Function

PAS has been researched as a method for functional motor recovery in both the upper and lower limbs of SCI individuals. Using PAS has been found to be superior to PNS alone (Pohjonen et al. 2021). There are many approaches to PAS interventions in the literature, in which stimulation parameters vary. These differences include targets (upper vs lower limb, specific muscle choices), treatment durations (single session vs multi sessions), and subjects (human vs animal studies) (Ling et al. 2020). Additionally—with SCI interventions—it is especially challenging to compare studies confidently, given the uniqueness of individual injuries. However, according to the current literature, it is common in PAS interventions target incomplete chronic injuries (Ling et al. 2020).

In human studies, the common method of brain stimulation for PAS protocols is TMS. While the instrumental tool remains the same, the intensity, pulse configuration, and coil type vary across studies. In most cases, studies determine the intensity based on the maximum stimulator

output (MSO) of the TMS device, while others determine it based on rMT (Ling et al. 2020). There are even some instances in which the stimulation is customized individually, as the "maximum tolerable intensity" of the MSO that the participant can handle (Pulverenti et al. 2022). Additionally, ISI calculation methods— all with the same goal of generating LTP— continue to be investigated. Older studies tested the series of set ISIs for all participants (Stefan et al. 2000, Taylor & Martin 2009), while more recent studies customize ISI to precisely target CST and cortical areas (Urbin et al. 2017, Shulga et al. 2021). Finally, calculations of PNS intensity and timing vary, based on maximum M-wave (Urbin et al. 2017) and F-response (Shulga et al. 2021). In all PAS approaches for SCI rehabilitation, the visualization of MEPs is required – which may not be in SCI patients, depending on their injury severity, as well as physiological neural tracts still intact (Ling et al. 2020).

A high intensity and high frequency PAS approach for SCI rehabilitation, known as high PAS, combines the positive effects of rTMS and PNS (FIGURE 5). rTMS alone requires high frequency stimulations, which over time can lower the patient's seizure threshold (Shulga et al. 2016). PNS is only effective for incomplete SCI patients, because it requires muscle activation to be successful (Pohjonen et al. 2021). Coordinating the two stimulation methods for PAS utilizes the mechanism of long-term plasticity. This novel approach of PAS has been validated using 100% of TMS MSO and a calculated ISI based on the individual MEP and F responses of the target muscles (Tolmacheva et al. 2019). This high intensity TMS and high frequency PNS approach encourages the LTP-like plasticity to overcome LTD-like plasticity, by increasing the number of interactions between the orthodromic and antidromic volleys (Shulga et al. 2016). This method also becomes more clinically feasible, as it can elicit MEPs at a wide range of ISIs (Shulga et al. 2016).

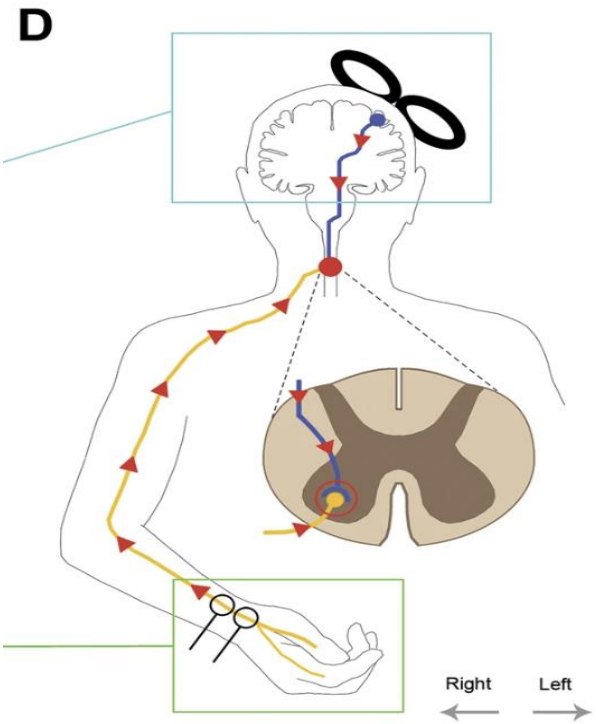

FIGURE 5: Simplified graphic of the neural mechanism of PAS targeting the CST for a muscle-nerve pair of the hand. Modified from Rodionov et al. (2019)

3 AIMS AND HYPOTHESIS

High PAS has been used in rehabilitation settings to facilitate long lasting improvements of hand motor output in the tetraplegic hand. These studies, including short-term (6-week) and long-term (one year) interventions, found varying degrees of long-term improvements in MEPs, grip force outputs, hand function tests, and manual motor scores in upper limbs (Tolmacheva et al. 2017, Rodionov et al. 2019).

The aim of this case study was to determine the clinical feasibility of a 6-week high PAS intervention to improve functional motor output—by means of MEPs, functional hand movement and strength clinical assessments—in the tetraplegic hand. The intervention has been proven successful for multiple incomplete tetraplegics within one research group, facility, and set up (Shulga et al. 2021). The current study will test the translatability of the protocol by using completely different equipment at a slightly different stimulation setting. This study will use a double cone coil at 80% MSO, instead of 100% MSO with a flat figure of eight coil, due to the greater power of the double cone coil (Drakaki et al. 2022). Additionally, the participant has a more severe injury than typical participants in this intervention. Thus, there are multiple variables that will test the feasibility of this high PAS protocol.

Research Question: Can a slightly modified version of high PAS protocol (using a 20% lower TMS intensity and a less focal coil), improve functional motor output of the chronic tetraplegic hand in a 6-week case study?

Hypothesis: A slightly modified version of high PAS will still yield positive effects on the motor function in the chronic tetraplegic hand.

4 METHODS

4.1 Patient Evaluation

This case study has been approved by the Ethics Committee of Medicine of the Helsinki University Hospital (appendix 1). The participant provided written informed consent for both the MRI and the treatment (appendix 2). One individual with traumatic chronic tetraplegia participated in the study. Based on the manual muscle test (MMT) (appendix 3), the left hand was more suitable for the study. A patient evaluation was performed 1 month prior to treatment, immediately post treatment, and 1-month post treatment. It consists of six categories of physiotherapy tests. These tests were administered by an experienced physiotherapist from the Helsinki region. The patient and assessor physiotherapist were native Finnish speaking, so tests were conducted in Finnish using Finnish forms. Some of them are official and some were modified, just to gather the information needed for evaluation. ASIA and SCIM are official and presented in English. The documents presented as appendices are translated to English for the purpose of the thesis, except for the consent forms.

The participant, 32-year-old male, has had a C5 level AIS scale C chronic spinal cord injury since 2018. An AIS scale of C means that the impairment is incomplete (the spinal cord is not fully transected, thus neural pathways still exist). There is residual motor function, but more than 50% of these muscles have a manual muscle score of less than 3 (see chapter 4.1.1). Before the intervention, the participant had been doing 60-minute physiotherapy sessions, two times a week, for the past 2 years. During the intervention, the participant decided to reduce the number of sessions due to the intensity of the intervention. He did not take active medicine affecting the CNS before, during or after the intervention.

4.1.1 Manual Muscle Test

The MMT is a manual procedure to assess joint motions (appendix 3). It is a well-known and frequently used method among physiotherapists to diagnose and assess movement impairments. The aim is to determine the individual's muscle contractile abilities, with a focus on impairment rather than strength. The limb muscles are categorized by each nerve root distribution. Each muscle contractile ability is assessed individually, by manually immobilizing others (Hislop et al. 2014). Scores range from 0 to 5: Zero/No Activity (0), Trace Activity (1), Poor (2), Fair (3),

Good (4), Normal (5). For this case study's purpose, the categories included in analysis are scapula, shoulder, elbow, forearm, wrist, fingers, and thumb.

4.1.2 ASIA Motor and Sensory Test

The ASIA is an assessment protocol to describe the functional impairment of an individual due to SCI (appendix 4). The full test consists of 1 sensory examination divided into sections based on the 28 dermatomes, 1 motor examination based on myotomes, and 1 anorectal examination. The full examination results are used to define the NLI, the AIS grade of injury classification, as well as the completeness of injury (Hospital 2011, 256). For this case study, only upper extremity sensory and motor impairment examinations were utilized, thus we did not categorize the NLI, but asked the participant for the information from the evaluation. Since the patient has a chronic injury, this does not change from diagnosis. The sensory examination assesses differential response to light touch and pin prick for spinal cord levels C2-T2 either 0 (absent), 1 (impaired) and 2 (normal). The motor examination assessed 5 upper extremity root levels, C5-T1, graded on a scale of 0 (total paralysis) to 5 (normal strength) (Hospital 2011, 256). Any change from 0 is a great improvement in SCI. The main aim is to standardize documentation of neurological level of injury and determination whether the SCI is complete or incomplete.

4.1.3 SCIM

The spinal cord independence measure (SCIM) is a disability scale designed specifically for spinal cord injury individuals (appendix 5). This measurement is used to interpret independence levels associated with daily life. The total score ranks on a scale of 0 to 100, with each of the listed categories (self-care, respiration, sphincter management, and mobility) having different scale ranges, depending on the proportional weight that the category has on general daily living. For example, respiration and sphincter management ranks 0 to 40, whereas self-care ranks 0 to 20. (Panuccio et al. 2021) Each category has subsections of daily responsibilities, which are each scored based on the individual's ability to carry out the task independently. For example, in the category of mobility, a subsection is "Transfers: bed-wheelchair", where a score of 0 is "requires total assistance", 1 is "needs partial assistance and/or supervision, and/or adaptive devices" and the highest score of 2 is "independent" (appendix 5). Any increase in the scale emphasizes an improvement in independence in its respective daily living activity.

4.1.4 Hand Function Tests

Hand function tests include box and block test, nine-hole peg test, hand function for activity of daily living (ADL) and grip/pinch strength (appendix 6 and 7). The Box and Block test is designed to measure unilateral gross manual dexterity. The individual must transfer blocks of the same shape and size one at a time across a partition and drop them on the opposite side. They have 60 seconds to transfer as many blocks as possible. For healthy male individuals aged 20-80, the average transfer of blocks is 77 blocks (left hand) and 75 blocks (right hand) (Mathiowetz et al. 1985-1). This test has long been considered the "gold standard" against other gross dexterity assessments (Desrosiers et al. 1994).

The Nine Hole Peg test is designed to assess finger dexterity. In the standard test, individuals must place small cylindric pegs into holes on a peg board, then remove them all after all holes have been filled. For the average healthy male, the test could be completed in 19.0 seconds (right hand) and 20.6 seconds (left hand) (Mathiowetz et al. 1985-2). This test has been modified for the SCI population. Rather than having to place all the pegs into the holes and remove them, they are timed for 60 seconds to place as many pegs as possible. (Backman et al. 1992). If the patient can finish the test in less than 60 seconds, then the time the test has taken is marked down and followed throughout the rehabilitation.

Grip strength tests were performed with a standardized Jamar Plus+ digital hand dynamometer. Grip width was positioned at the standard position of 3 for males. The individual must have the elbow flexed to 90 degrees (or as close as possible), with the arm positioned to their side. The individual has 3 attempts, and the highest strength is recorded. (Ewing 1992). For the average healthy male, age range 30-34 (same range as the participant), the normative grip strength scores for the right hand are 55.2 ± 10.2, and the left hand 49.9 ± 9.8 kg (Mathiowetz et al. 1985-3). Finger pinch tests—index and thumb pinch, key pinch, and a three-finger pinch—were performed with a pinch gauge. The sitting position is the same as the grip strength test. The individual has 2 attempts with 30 seconds in between, starting with the dominant hand. (Stegink et al. 2003) For the average healthy male, age range 30-34, normative values for index and thumb pinch strength in the right hand are 7.9 ± 3.0 and 7.9 ± 2.2 in the left hand. Key pinch

scores in the right hand are 11.9 ±2.2 and 11.9 ± 2.3 in the left hand. Three-finger pinch scores in the right hand are 11.2 ± 2.1 and 11.5 ± 2.6 in the left hand (Mathiowetz et al. 1985-3).

Finally, ADL (appendix 6) assesses the ability to perform functional tasks in daily life. Among these tasks include opening a water bottle, buttoning a shirt, slicing bread, and others. The participant is given the tools to complete the task and there is no time limit to complete them. They must be able to complete the task independently. Each task is scored as a 1 or 0 (1 = yes, can complete the activity, 0 = no, cannot complete the activity).

4.1.5 Modified Ashworth Scale

Modified Ashworth Scale (MAS) was used to measure spasticity in the right and left sides of the upper extremities (appendix 8). Spasticity is an involuntary muscle activity seen in SCI cases and is brought on by a hyperactive stretch reflex that increases muscle tone (Dunning 2011, 255). The test involves the physiotherapist manually moving each joint through a passive full range of motion and rates the perceived level of resistance of the limb during the motion. The scale of the test is from 0-4, with 0 = no increase in muscle tone and 4 = limb rigid in flexion or extension. (Dunning 2011, 254). Physiotherapist can decide to include a 1+ score between 1 and 2. This method doesn't fully encompass all aspects that affect spasticity but is the most common assessment tool for this demographic.

4.1.6 Pain Questionnaire

The pain questionnaire used can be found in appendix 9. It is from the International Spinal Cord Injury Pain Basic Data Set, version 3.0. This evaluation is an accessible and standardized method to assess specific pain complications as well as multiple pain problems. Pain is defined as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage" (Raja et al. 2020). If no pain is present, the score is 0 (scale 0-36). If pain is present, there are 3 interference factors to further understand the pain's effect on daily activities, mood, and sleep. For example: "Usually, how much did the scale bother your daily activities last week?", and they should answer on a scale of 0 (no pain) to 10 (worst pain you can imagine). Finally, location and type of pain are determined.

4.2 Study Design

PAS was given to both left and right hands, targeting 6 muscles of the hand/fingers, paired with their equivalent nerve. The following muscle-nerve pairings were targeted: abductor digiti minimi (ADM) with ulnaris nerve, extensor digitorum (ED) with radialis nerve, and abductor pollicis brevis (APB) with medianus nerve. PAS parameters were determined with TMS and peripheral nerve stimulation measurements. TMS measures include MEP latency and MEP average at 80% of the TMS stimulator output/maximum stimulator output (MSO). PNS measures include F-response latency and intensity. These were used to calculate the ISI. Calculation measurements were done 1 and 2 days prior to the first therapy session.

The 6-week intervention includes 22 total therapy sessions (5 days per week for 2 weeks and 3 days per week for 4 weeks) (TABLE 1). Each session took 20 minutes per muscle-nerve pairing, as each pair gets 240 TMS trains 5 seconds apart.

TABLE 1: Stimulation Parameters and Schedule

<table>
<tr><td colspan="3">6 WEEKS: 22 PAS SESSIONS</td></tr>
<tr><td colspan="2">2 Weeks: 5 Days a Week</td><td>4 Weeks: 3 Days a Week</td></tr>
<tr><td>Pair 1: 240 Pairs of PAS Trains</td><td>Pair 2: 240 Pairs of PAS Trains</td><td>Pair 3: 240 Pairs of PAS Trains</td></tr>
<tr><td colspan="3">2 Hand per Session</td></tr>
<tr><td colspan="3">STIMULATION PARAMETERS:</td></tr>
<tr><td colspan="3">PNS: 100Hz. Minimum intensity to produce an F response. 6 biphasic square-wave 1ms pulses. 100ms trains.
TMS: 80% stimulator output. single 0.2 Hz pulses. Biphasic. Double Cone Coil.</td></tr>
<tr><td colspan="3">ISI: MEP latency – F-latency</td></tr>
</table>

4.3 Mapping Sessions

Calculation sessions took place during the 2 days prior to the therapy sessions. Day 1 was for mapping the motor hotspots of the 6 hand muscles using a navigation system (Localite, Bonn, Germany). The magnetic stimulator (Magventure, Farum, Denmark) was combined with

Magventure Cool-DB80 cooling double cone coil. This combination was used in all steps of the case study. sEMG data was recorded using BlueSensor N-00-S/25 disposable Ag/AgCL sensor electrodes, with a 95mm^2 sensor area (Ambu, Ballerup, Denmark). Sampling frequency was at 2000 Hz, and bandwidth was between -2.5V and +2.5V. EMG was amplified at 50 gain. This is the universal gain for the EMG imaging system, the multifunctional NeurOne system (Bittium, Oulu, Finland). The main electrode (proximal) was placed over the muscle belly, which was palpated while the participant was asked to perform a contraction (if it were possible). The reference electrode (distal) for each muscle was based on the anatomical landmarks of the metacarpal and phalangeal joint spaces (ADM/APB), and the ganglion (ED). Ground electrode was placed on the bony surface of the pronated hand. Skin was prepared by first abrading the skin with sandpaper, then wiping the surface with a cloth soaked in alcohol disinfectant (Hermens et al. 1999). Shaving was determined not mandatory, because the locations used do not have much hair. Sandpaper was only applied every 3 sessions. sEMG location sites can be seen in (FIGURE 6).

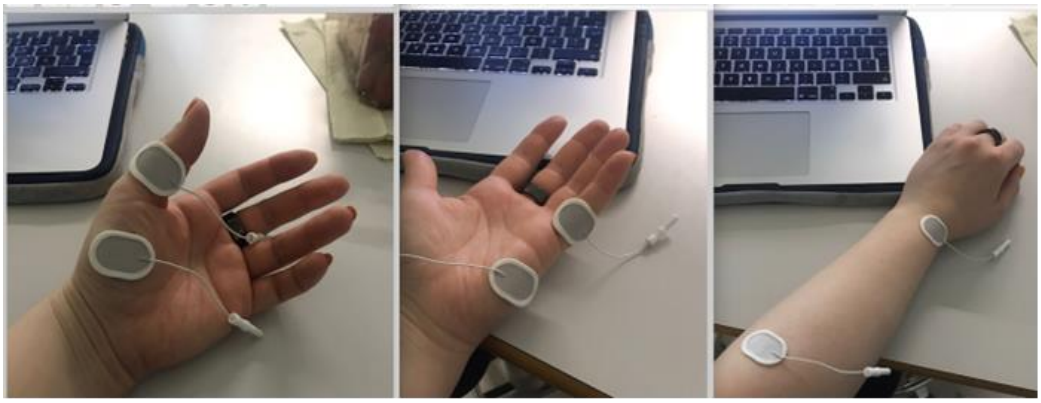

FIGURE 6: sEMG sites (different electrodes). Left to right: APB, ADM, ED.

Mapping started with the left hand (APB, then ADM, and ED), followed by the right hand in the same muscle order. The left hand was chosen first for reference, due to the lower MMT scores of right hand. MEP signals were image the using the NeurOne system with the EMG electrodes. Hotspot was defined as the area of the motor cortex that yielded the highest MEP amplitude, with the target muscle movement. MEPs were prioritized, even if the muscle response was greater in another brain mapping spot. The participant was instructed to practice motor imagery to facilitate MEP response. Example muscle contractions were demonstrated for each muscle.

Once the hotspot was identified, we took the average MEP amplitude from 15 consecutive (5 seconds between each pulse) TMS stimulations at 80% MSO. This more tolerable intensity with the double cone coil—compared to 100% MSO with the flat figure of eight coil—was determined based on both the participant's "maximum tolerable intensity" and the electric field strength information of the coil used in this study (Magventure Cool-DB80) compared to the coil used in the model study (navigated cooled figure-of-eight coil (Nexstim Ltd., Helsinki, Finland)) (Drakaki et al. 2022). The MEP image was saved. The MEP latency in milliseconds was calculated from the averaged MEP. MEP latency is identified as MEP wave onset.

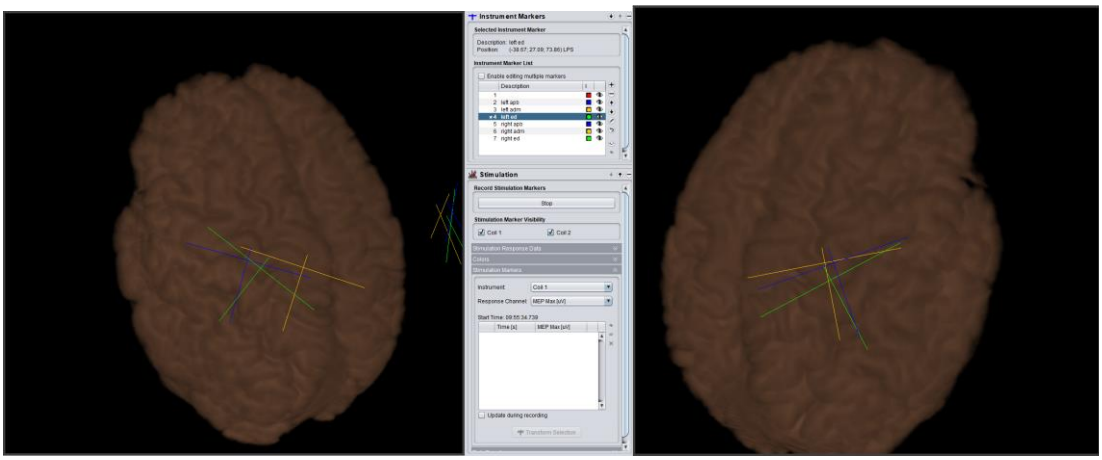

FIGURE 7: Hotspots for left and right APB (blue), left and right ADM (orange), and ED (green) of the left and right hemisphere.

F-response was measured on day 2 using the (Digitimer Letchworth Garden City, UK) 2700 electrical stimulator. The same EMG electrodes were used with the stimulator and sEMG. sEMG placements were replicated from the previous session using a visual reference for repeatability (FIGURE 8). NeurOne system was used to image F-response waves. F-response latency and intensity were found for the ulnaris, medianus, and radialis nerve. Radialis nerves of both hands were highly responsive to pressure on the posterior face of the humerus, more predominantly in left compared to right.

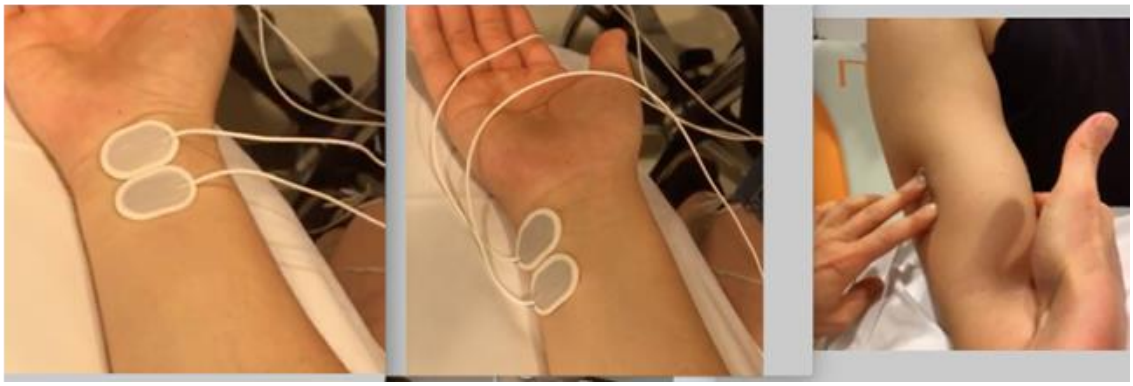

FIGURE 8: Nerve stimulation spots (different electrodes). Left to right: Medianus, Ulnaris, Radialis.

To find F-response latency, stimulation settings were 0.2 ms pulse length and 1 Hz frequency. Stimulations started at 1mA, then increased until F-response amplitude plateaued (approximately 20 μV). To find the PNS intensity, stimulation settings were 1.0 ms pulse length and 1 Hz frequency. Stimulations started at 1mA and increased until close to threshold intensity. Threshold intensity was defined as at least 1 visible F-response out of 10 stimuli. The threshold was confirmed with 0.5 mA accuracy. Intensity was recorded in mA as the PNS intensity for PAS. ISI was calculated with the equation: MEP latency – F latency. The calculated value was programmed into Spike2 (Cambridge Electronic Design Ltd., UK) computer software, using the graphical sequencer function (FIGURE 9). This function allows for precisely timed stimulation loops to be repeated, ending at the 240th TMS train.

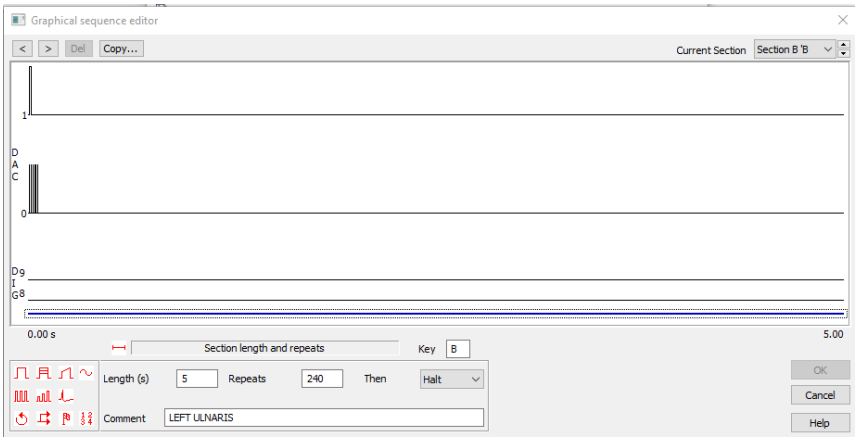

FIGURE 9: DAC 1 represents the TMS trigger and DAC 2 represents the PNS trigger. PNS train is programmed before or after TMS (based on ISI), and all muscle-nerve pairs repeat their

respective order of stimulation. This is repeated every 5 seconds for 240 TMS pulses, totaling 20 minutes.

One compromise had to be made for left medianus' ISI. Spike2 software's graphical sequencer creates a "timing fault" for ISI's within the range of -1–1ms. If the ISI is programmed within this range, Spike2 will run the graphical sequence "as close as possible" to the ISI. Thus, we ran a pilot PAS session using an ISI within the timing fault sequence. The session was recorded, and vertical cursor regions defined the ISI difference between TMS and PNS pulses. The timing fault made the ISI 1.2ms. We accept and justify the .2ms positive error. A second compromise was determining the F response latency for left abductor pollicis brevis. The shortest was 32ms, but the latency response was consistently 33.2ms, so we accepted this value instead. Stimulation parameters recorded from this session is in (TABLE 2).

TABLE 2: Stimulation parameters and movement/motor imagery instructions.

Stimulation parameters and movement instructions						
Side	Nerve	PNS (mA)	F (ms)	MEPs (ms)	ISI (ms)	Instructions
Right	Median	4	32	34.5	-2	Imagine pinching thumb, index, and middle finger together before the TMS pulse, relax after pulse
	Ulnar	12.5	33	36	-3	10 min: Imagine bending IV-V fingers to palm before the pulse, relax. 10 min: Imagine spreading fingers before the pulse, relax
	Radial	6	12	18	-6	Lift wrist before the pulse, lift fingers before the pulse, relax
Left	Median	5	33.2	32	1	Pinch thumb, index, and middle finger together before the TMS pulse, relax after pulse
	Ulnar	9.5	34.4	36.5	-2	10 min: Bend IV-V fingers to the palm before the pulse, relax. 10 min: spread all 5 fingers before the pulse, relax
	Radial	28	16	21.4	-5	Lift wrist before the pulse, lift fingers before the pulse, relax

4.4 Stimulation Sessions

The hotspots identified with the Localite nTMS system were saved under the patient's MRI file. Each stimulation session used the exact hotspot location for each muscle to ensure accuracy over repeated stimulation sessions. When holding the coil, maximum alpha and beta error was maintained under 3mm, with total gamma error under 20mm. Gamma error in Localite system was defined as total error distance from coil orientation to the identified instrument marker. The

cone shape of the Cool-DB80 has a 50 mm distance from midpoint to scalp, thus the reason for this greater distance of total gamma error.

Spike2 had shortcut keys for each PAS sequence, labeled A-F (as seen in figure X above). Sequences were programmed to trigger 240 stimulation pairs and halt at the end. Peripheral stimulation intensity was changed manually via Digitimer dial. One practitioner was responsible for changing the PAS settings (Localite, Spike2, and Digitimer) after each 20-minute stimulation, while the other was responsible for removing and changing stimulating electrode placements.

The participant was instructed at the beginning of each session to practice motor imagery and muscle pre-activation during the sessions. The timing of motor imagery and muscle pre activation should be immediately before the pulse and then fully relaxed after the pulse.

A body pillow was fastened to the chair to support the arms into a rested position. An extra standard size pillow was positioned under the arm during radialis stimulations to reduce the impact of muscle reaction. During the radialis stimulations, one assistant would apply pressure to the electrode to ensure optimal connection, while also blocking the hand from rebounding uncontrollably without forcibly resisting the movement. The other assistant held the TMS coil in place. For the other two nerve/muscle stimulations, just one assistant was needed to hold the coil in place. Session preparation takes about 20 minutes to place stimulating electrodes and Localite forehead marker on the participant. Localite patient registration and coil calibration took about 10 minutes each time, making each session about 2 hours and 40 minutes.

When working with clinical populations, it is vital to understand patient risk factors, monitor wellbeing during treatment, and have a plan of action in case of medical emergency. All research assistants were familiarized with the possible warning signs of autonomic dysreflexia (Krassioukov et al. 2009). If a SCI individual doesn’t regularly experience autonomic dysreflexia, they are less likely to have an episode in the future. Our participant does not normally experience this, but we were aware of the proper procedure. A blood pressure cuff was available to use in the next room in case of necessary monitoring. Special attention was directed to ensuring participant comfort during sessions. The participant was informed he can

stop the treatment at any time. Emergency information was printed clearly for assistants to follow in case of a medical emergency.

5 RESULTS

5.1 Physiotherapy Assessments

Spasticity according to MAS maintained a score of 0 for the upper body. Similarly, the participant's pain scores started at 0 and stayed at 0. ASIA total motor scores changed in the left but not the right hand. Left hand values from baseline, 6 weeks, and 1 month follow-up were 16/14/17, and the right hand were 10/10/10. A normally functioning motor score for the measured dermatomes would be 50. ASIA sensory scores changed in both limbs and for both light touch and pin prick tests. For the light touch test, left hand values from baseline, 6 weeks, and 1 month follow-up were 12/13/14 and the right hand were 12/14/15. For the pin prick test, left hand values from baseline, 6 weeks, and 1 month follow-up were 7/13/11 and right hand values were 8/11/7. A normally functioning sensory score for the measured dermatomes would be 18 (FIGURE 10).

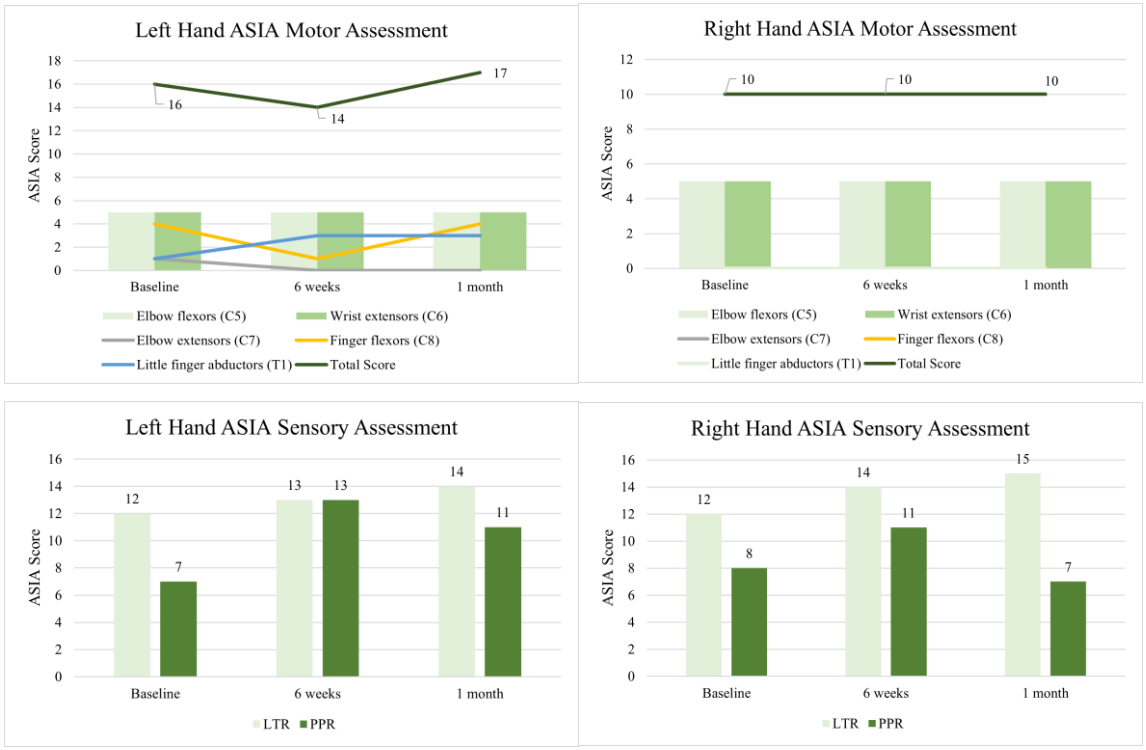

FIGURE 10: Left and right hand ASIA motor and sensory scores (LTR=light touch/PPR=pin prick)

The pain questionnaire scores also didn't change as they started at 0. Total MMT scores increased in both hands. All stimulated nerve MMT scores (radial, median, ulnar) increased in

the left hand, while right hand stimulated nerve MMT scores improved in just the muscles innervated by the radial and median nerve. Total MMT scores were compared to MMT scores of the muscles targeted by the stimulation. In the right hand, the total score increased from a baseline of 69 to 76 at the 1-month follow-up. In the muscles targeted by the stimulation, there was an increase from 14 at baseline to 18 at the 1-month follow-up. In the left hand, the total score increased from a baseline of 107 to 125 at the 1-month follow-up. In the targeted muscles, there was an increase from 51 at baseline to 68 at the 1-month follow-up. (FIGURE 11).

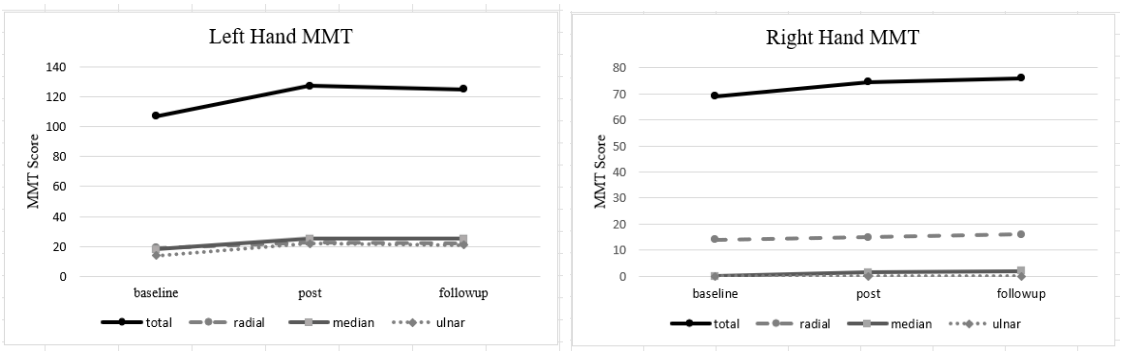

FIGURE 11: MMT scores of the left and right hand. Individual MMT scores of muscles associated with the nerves targeted in the PAS intervention (radial, median, ulnar).

All grip and pinch strength tests in the left hand showed improvements at both the 6-week mark and the 1-month follow-up. Grip strength in the left hand improved by nearly twice the baseline strength of 6.1kg. At 6 weeks, grip strength was 11.2kg, then 11.8kg at the 1 month follow up. Index finger and thumb pinch increased from 0.5kg at baseline to 1kg at 6 weeks and sustained for follow-up. Key pinch increased from 1.25kg at baseline to 1.5kg at 6 weeks but returned to baseline at the follow-up. Finally, the three-finger pinch increased from 0.5kg at baseline to 1kg at 6 weeks and dropped to 0.75kg at the 1-month follow-up (FIGURE 12). There were no improvements in the right hand for grip and pinch strength tests.

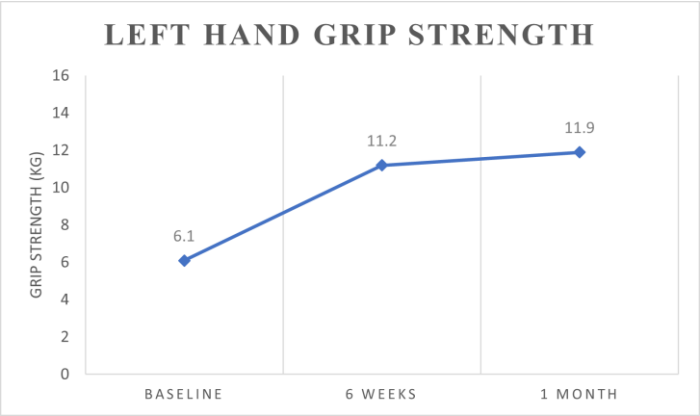

FIGURE 12: Left hand grip strength test changes from baseline, immediately post (6-weeks), and 1-month follow-up.

Box and block test scores increased from 12/32 (right/left hand) at baseline, to 22/34 at 6 weeks, then 24/33 at the one-month follow-up. The 9 hole-Peg test changed scores went up and down for both hands, from 0/4 (right/left hand), to 1/2 at 6 weeks, and 0/7 at the one-month follow-up (FIGURE 13).

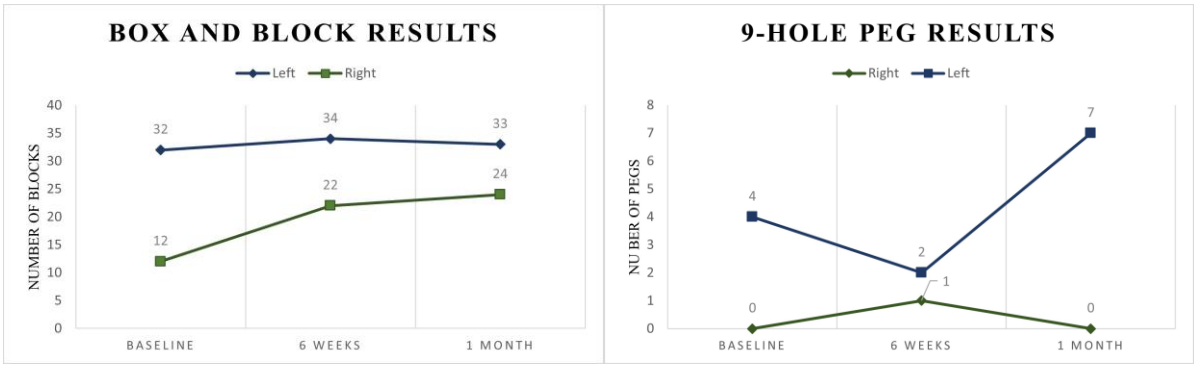

FIGURE 13: Box and block and 9-hole peg test change from baseline, immediately post (6 weeks), and 1-month follow-up.

In hand function tests for ADL, the left hand maintained the score of 1 in all activities throughout all assessment periods. The right hand could only complete 2 tasks successfully at baseline (spoon use and using a tablet to write their name). At 1 month follow-up, the participant could additionally complete 3 more tasks (cutting bread, reaching, and taking an object from the diagonal direction, and opening a lock of a door) (TABLE 3).

TABLE 3: Hand functions in activities of daily living change from baseline, immediately post (6 weeks), and 1-month follow-up.

Hand functions in activities of daily living			
Right Hand	Baseline	6 weeks	1 month
Spoon use	1	1	1
Cutting bread	0	1	1
Bottle opening, spiral cap	0	0	0
Pouring water from bottle to glass	0	0	0
Drinking water from glass	0	0	0
Taking object from diagonal direction (reaching)	0	1	1
Buttoning and unbuttoning 3 buttons (both hands)	0	0	0
Pencil grip and drawing a triangle	0	0	0
Using a pad/tablet and writing a name with it	1	1	1
Opening a lock (bathroom door)	0	0	1
Left Hand	Baseline	6 weeks	1 month
Spoon use	1	1	1
Cutting bread	1	1	1
Bottle opening, spiral cap	1	1	1
Pouring water from bottle to glass	1	1	1
Drinking water from glass	1	1	1
Taking object from diagonal direction (reaching)	1	1	1
Pencil grip and drawing a triangle	1	1	1
Using a pad/tablet and writing a name with it	1	1	1
Opening a lock (bathroom door)	1	1	1
(0) no (1) yes			

SCIM scores improved in the movement section, from baseline to 6 weeks, and were sustained at the 1-month follow-up. “Mobility in bed and action to prevent pressure sores” went from a score of 4, to the highest score of 6, and “Transfers; wheelchair-toilet-tub” went from a score of 0 to 1. Total SCIM score went from 57 to 60 (FIGURE 14).

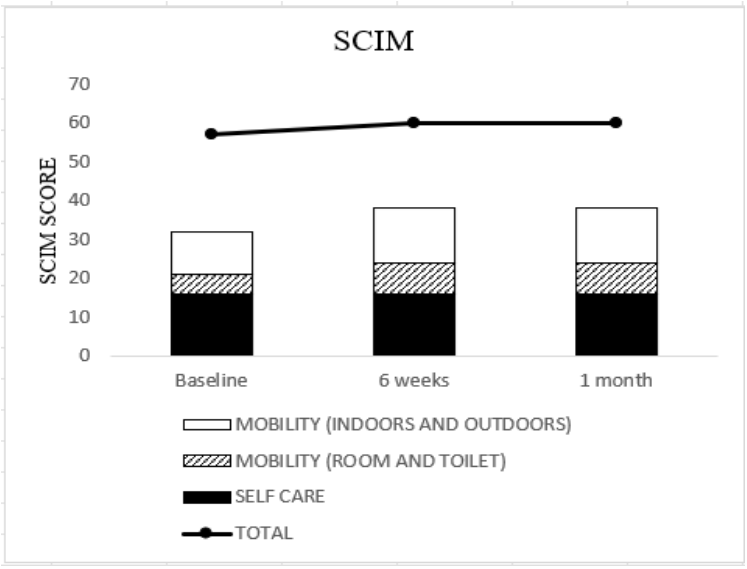

FIGURE 14: SCIM assessment changes from baseline, immediately post (6 weeks), and 1-month follow-up.

5.2 MEPs

TMS elicited clear MEPs in four out of the six targeted muscles. The two right hand muscles which didn't have clear MEPs were likely due to their location below the NLI. The greatest increase from pre-to-post MEPs measurements were seen in both right and left ED (TABLE 4). Raw MEP images can be found in the appendix (appendix 10).

TABLE 4: MEPs (in microvolts) change from baseline to immediately post (6 weeks).

	MEPs (80% MPO)		**Change**	
TARGET	**PRE (mV)**	**POST (mV)**	**Absolute (mV)**	**Relative (%)**
LEFT APB	320	310	−10	−3%
LEFT ADM	150	150	0	0%
LEFT ED	150	490	340	227%
RIGHT APB	-	-	-	-
RIGHT ADM	-	-	-	-
RIGHT ED	100	480	380	380%

6 DISCUSSION

6.1 Physiotherapy Results

ASIA motor scores in the left had little finger abductors (T1) sustained an increase from 1 (visible contraction) to 3 (active movement; full ROM against gravity). All other tested dermatomes either remained the same level or returned to baseline. ASIA motor scores in the right hand saw no change. In this case, it could consider this a positive result and accurate considering the improvements in dexterity in the left hand. There were increases and decreases in ASIA sensory (light touch and pin prick) scores for some dermatomes in both the left and right hand. There did not seem to be a specific trend in certain dermatomes increases or decreases in sensation. For example, C6 dermatome on the right hand saw an increase (1 at baseline and 2 at 1 month follow-up) in the light touch test. At the same dermatome there was a decrease in the pin prink score (2 as baseline and 0 at 1 month follow-up). Thus, the ASIA sensory scores could be considered inconclusive. It seems that inconsistency is common with this type of intervention as it has been reported before (Shulga et al. 2016). More testing should be conducted more frequently to be confident in the outcome of these results.

It was expected that MAS nor Pain Questionnaire results would change, since the baseline values were both 0. No pain or spasticity was caused due to the intervention. The lack of effect on spasticity has been a trend with this protocol of PAS (Tolmacheva et al. 2017; Shulga et al. 2016). The SCIM questionnaire, which determines the functional mobility of the individual, and each single score increase should in theory indicate a positive impact in daily living. The increases were in areas of mobility indoors and outdoors, specifically related to transfers and mobility in bed and chair. This was a surprising improvement for such a short-term intervention, compared to the first reported sustained increase in SCIM being a long-term intervention (Rodionov et al. 2019). “Mobility in bed and action to prevent pressure sores” went from the score of 4 “performs two or three of the activities without assistance” to 6 “performs all the bed mobility and pressure release activities independently”. After this intervention, the participant was able to become functionally independent in bed and pressure sore prevention mobility. “Transfers: wheelchair-toilet-tub” went from the score of 0 “requires total assistance” to 1 “needs partial assistance and/or supervision, and/or adaptive devices”. This change shows an increase in independence for self-care. Thus, even small changes in SCIM scores indicate

improvements in independence for activities of daily living. For those with a SCI, mobility is a high priority in rehabilitation towards functional independence (Duan et al. 2021).

MMT increased in both targeted and non-targeted muscles. However, the improvement was greater in the left hand. This is in line with previous studies, that have reported higher base line motor scores led to greater functional improvements post intervention (Tolmacheva et al. 2017). This correlates to the greater improvements seen with the left hand that are discussed below.

Grip strength in the left hand showed an impressive increase, and while still below the normative values, the grip strength doubled, possessing an optimistic functional application. The ability to firmly grasp objects makes tasks, for example—picking up objects—easier to perform. Pinch strength improved for the left hand, but not the right hand, as the right hand could not accurately perform the grip or pinch tests. This result contributes to the value that upper extremity PAS rehabilitation can be more valuable to SCI patients. It is more valuable to be able to do functional tasks to make daily routines easier to perform (Duan et al. 2021). From the participant's perspective, he felt that the left hand was easier to use, given its increase in strength.

Box and Block is representative of gross manual hand dexterity, thus the left hand already had prior functionality according to the manual muscle test. The greatest improvements were seen with the right hand as it doubled in score. Nine Hole Peg test showed improvement in the left hand, not in the right. This is most likely because this test focuses on the fine dexterity function, and the intervention was not as effective for the right hand muscles in fine dexterity innervating muscles. Hand function in ADL saw a sustained increase for 3 tasks in the right hand. This included cutting bread, taking an object from the diagonal direction, and opening a bathroom door lock. Compared to baseline, he is now able to complete these 3 tasks independently. This could be attributed to the better results seen with the right ED from high PAS, as well as the Box and Box results, as these tasks—while they do require finger dexterity—can be done with increased mobility of lifting the wrist/fingers.

6.2 MEP Results

Based on the MEP differences from baseline to post, the ED saw the most improvements for both hands. This is most likely due to the MMT scores at baseline being higher for the muscles innervated by the radial nerve. For the ADM and APB of the right hand, it made since that MEPs were not visible baseline or post due to the lack of MMT and visibility of MEPs at baseline. Based on the MEP results, one could consider the intervention to only be beneficial to the left and right ED. However, it is important to highly consider the physiotherapy outcome measures, as these show the functional advantages brought on by this intervention.

6.3 Methodological Limitations

6.3.1 Protocol Differences

The original study protocol administered TMS with using an eXimia (Nextim, Helsinki, Finland) magnetic stimulation with a cooled flat figure-of-eight coil, with an outer loop diameter of 70mm. The current study administered TMS using a MagVenture magnetic stimulation, with a cooled double-cone coil, with an outer loop diameter of 95mm. The differences in coil design allude to different electric field characteristics. Thus, one consideration should be the difference between two coils' depth vs focality tradeoff (Drakaki et al. 2022). While the double-cone coil allows deeper stimulation and encompasses a greater scope of the brain, so it manages to target the already more superficial hand muscle.

Additionally, if the double-cone coil is to be used in the future for this type of intervention, it could be advantageous to test a TMS intensity based on the motor threshold. Since the double-cone coil can stimulate a greater volume of cortical gray matter and it simulates deeper in the cortical structure, it should be able to stimulate at lower intensity with similar results compared to a flat figure-of-eight coil. The double-cone coil at high intensities can pose a safety risk as well as discomfort or even pain to the participant. Thus, it would be advantageous to explore the lowest possible intensity to induce the same positive outcomes. While this case study design and the model protocol determines the TMS intensity based on the MSO, one consideration could be to determine the intensity as a percentage of the rMT.

It has yet to be determined what approach to determining TMS intensity for PAS protocols yields the most advantageous results (Ling et al. 2020). With high PAS, it is based on the principle that the higher the intensity of TMS stimulation and PNS frequency, the greater number of collisions between descending and ascending volleys, therefor overcoming the LTD-inducing stimulations (Shulga et al. 2021). A question to explore is how high, is high enough for this PAS protocol? The current case study shows that it is possible to achieve improvements with a lower MSO, showing that it can be more clinically feasible.

With these considerations, we improved the validity of the different intensity and coil used, by conducting a secondary validation study after the case study. Four healthy individuals received PAS at 80% MSO with the double-cone coil to replicate this current case study's design. PAS significantly increased MEPs in all four individuals, reassuring the validity of using 80% MSO in this case study, compared to the 100% MSO used by Rodionov et al. (2017).

6.3.2 Study Design Limitations and Future Considerations

While this study replicated a 6-week protocol, the literature has more successful studies with continued stimulations for chronic patients. For example, a 3-month, 6-month, 1 year follow-up physiotherapy evaluation alluded to the longer-term effects of the intervention (Tolmacheva MEP results could have been more thorough, if we measured at 30 minutes post and 60 minutes post PAS, as excitability acts differently individually (Mezes et al. 2020). In some individuals there is a peak in MEP amplitude immediately post, while others continue to increase their MEP response even 60 minutes post (Mezes et al. 2020).

Many factors within the lab could influence the effectiveness of PAS. These include time of day, attention and alertness, and sleep deprivation (Minkova et al. 2019). Alertness, for this type of intervention, could have had the most effect (out of aforementioned factors), given the long duration of each session. The subject was instructed throughout the session to practice the motor pre activation and motor imagery, but even with the instruction the subject could lose attention easily. This is why the order of muscle stimulation was rotated so that the results due to alertness could be mitigated.

Regarding the equipment, there is the potential for more precise TMS. Multi-locus TMS is a

new stimulator being developed which involves overlapping coils (Koponen et al. 2018). By using this for a PAS protocol, switching stimulation spots between muscles would not require any moving of the coil. This could make the sessions more comfortable (not moving a cumbersome coil around the head) and improve its efficiency.

Another consideration would be to supplement the PAS treatment with a type of visual feedback training. Visual feedback training and mirror therapy are frequently used methods in stroke rehabilitation (Sütbeyaz et al. 2007; Cheng et al. 2023). A pilot study has been conducted combining rTMS and visual feedback training during ankle rehabilitation sessions. Their results showed promising modulations of corticospinal excitability, improving the efficacy of the intervention (Cheng et al. 2023). However, larger sample sizes are needed to validate this finding further. Therefore, it would be advantageous to study this with PAS and SCI.

To see a greater increase in the outcome measures and to improve the perceived value of the treatment to the participant, it would be recommended to continue the treatment for longer than 6 weeks. Previous experiments treat chronic tetraplegic patients for periods of 3 to 5 months, and in some cases a full year of treatment, as there continued to be improvements (Shulga et al. 2021). This is logical due to the Hebbian rule for neuroplasticity, which anticipates longer lasting change in neural circuits when the stimulation duration is extended (Ling et al. 2020). If this treatment could continue to be implemented for longer periods of time and to multiple patients at a time, it could have a greater impact to the SCI population in Finland.

7 CONCLUSION

The main finding is that the PAS 6-week protocol works with a similar yet slightly altered stimulation design and laboratory equipment. Changes were positive and more effective in the left hand. This was predicted due to the baseline conditions of the left and right hand before starting the protocol. Based on the results presented in the case study, the hypothesis can be accepted, as positive effects to motor function were found. This high PAS protocol has potential for clinical feasibility. To get greater results for a chronic state of injury, the total number of stimulation sessions should be increased.

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8 APPENDICES

Appendix 1: Ethical Approval

HELSINGIN JA UUDENMAAN SAIRAANHOITOPIIRI	Lausunto	1 (1) asianumero: HUS/1280/2016 tehtävä: 13.02.01
Tutkimuseettiset toimikunnat	9.7.2019	Salainen

Anastasia Shulga

Synkronoitu magneetti- ja sähköstimulaatio selkäydinvauriopotilaiden kuntoutuksessa

Viite	HUS/1280/2016
	HUS eettinen toimikunta I käsitteli tutkimussuunnitelmanne kokouksessaan 19.6.2019 § 102 ja pyysi siihen korjauksia. Toimikunnan valtuuttamana puheenjohtajalla on valtuudet hyväksyä toimikuntaan saapuneet pyydetyt korjaukset ja lisäselvitykset.
	Tutkimussuunnitelman pyydetyt korjaukset ja lisäselvitykset käyvät ilmi toimitetuista asiakirjoista: kts. liitteet
	Tutkimussuunnitelma ja sen liitteet täyttävät tutkimuslain (488/1999) 17 §:n 3 momentin mukaiset edellytykset.
Päätös	Toimikunnan puolesta puheenjohtaja päätti hyväksyä pyydetyt korjaukset/ lisäselvitykset ja antaa niistä puoltavan lausunnon.
	Toimikunnan pyytämät korjaukset, lausunto on maksuton (STM:n asetus 1287/2018, 1 § 3 mom).
	Vakuudeksi
	Helsingissä
	Johan Marjamaa puheenjohtaja

Liitteet

Saatekirje_korjaukset.pdf
HUS-1280-2016-17 Lausunto Eettinen toimikunta I 19.06.2019 §102
520700_2_0.pdf
Liite 9 Tutkittavan_tiedote_ subakuutit hoito_korjattu.pdf
subakuutit aikataulu.xlsx

Appendix 2: Written consent forms (in Finnish)

1. MRI Consent Form

Magneetti- ja sähköstimulaatio selkäydinvauriopotilaiden kuntoutuksessa

Tutkimuksesta vastaava henkilö: Anastasia Shulga, HUS, puh nro 0503462983
Tutkimuspaikka: HUS
Tutkittavan nimi:_____
Henkilötunnus:_____
Osoite:_____

TUTKIMUSPOTILAAN SUOSTUMUS RAKENTEELLISTEN MRI-KUVIEN OTTAMISEKSI

Tässä tutkimuksessa transkraniaalinen (kallon läpäisevä) magneettistimulaatio (TMS) suunnataan tarkasti halutulle aivoalueelle käyttäen apuna tutkimuspotilaan rakenteellisia MRI-kuvia. Järjestelmän avulla nähdään miten paljon stimulaatiota kohdistuu kullekin alueelle aivoissa, jolloin stimulaation vaikutus saadaan kohdistettua juuri haluttuun paikkaan.

Tutkimuspotilaista otetaan rakenteelliset MRI-kuvat ennen kokeellista hoitoa, mikäli tarkoitukseen sopivia kuvia ei jo ennestään ole. Kokenut lääkäri käy läpi kuvat ja mikäli magneettikuvissa havaitaan sairauteen viittaavia löydöksiä, hän keskustelee tilanteesta tutkimuspotilaan kanssa. Mikäli tutkimuspotilas ei halua tietää mahdollisista sairauteen viittaavista löydöksistä, häntä ei kuvata MRI- laitteistolla, eikä hän voi myöskään osallistua tutkimukseen.

Merkitse rasti ruutuun:
□ Olen lukenut tämän tiedotteen ja haluan, että minulle kerrotaan, mikäli MRI-kuvistani havaitaan sairauteen viittaavia löydöksiä.

Helsingissä / 20___

_____
Tutkittavan allekirjoitus

_____
Suostumuksen vastaanottajan allekirjoitus

2. Participation Consent Form

Tutkijalle/tutkittavalle

Synkronoitu magneetti- ja sähköstimulaatio selkäydinvauriopotilaiden kuntoutuksessa

Tutkimuksesta vastaava henkilö: Anastasia Shulga, HUS, puh nro 0503462983
Tutkimuspaikka: HUS
Tutkittavan nimi: _____
Henkilötunnus: _____
Osoite: _____

Kätisyys: ☐ Oikea ☐ Vasen

TUTKIMUSPOTILAAN SUOSTUMUS

Vastatkaa seuraaviin kysymyksiin (kyllä/ei) merkitsemällä rasti ruutuun. Mikäli jokin kohdista pätee kohdallanne, kokeellista hoitoa ei voida antaa.

	Kyllä	Ei
Onko kehossanne metallisia esineitä (muita kuin hammaspaikat/ leikkauksessa käytetty materiaali)?	☐	☐
Onko kehossanne elektronisia laitteita (sydämentahdistin, kuulokoje)?	☐	☐
Onko teillä merkkejä nousseesta kallonsisäisestä paineesta? (päänsärkyä ja oksentelua erityisesti aamuisin, kaksoiskuvia)	☐	☐
Onko teillä todettu epilepsia?	☐	☐

Vastatkaa seuraaviin kysymyksiin (kyllä/ei) merkitsemällä rasti ruutuun. Mikäli jokin kohdista pätee kohdallanne, tulee teidän keskustella tutkimuksesta vastaavan henkilön kanssa siitä, voidaanko kokeellista hoitoa antaa.

	Kyllä	Ei
Onko teillä todettu jokin hermoston sairaus (muu kuin selkäydinvamma)?	☐	☐
Onko teillä todettu jokin sydänsairaus?	☐	☐
Onko sisaruksillanne, vanhemmillanne tai isovanhemmillanne ollut epilepsiaa?	☐	☐

Mikäli aivoistanne tehdään tutkimuksen aikana sairauteen viittaavia löydöksiä, kokenut lääkäri arvioi tilanteen ja keskustelee siitä kanssanne. Mikäli ette halua tietää mahdollisista sairauteen viittaavista löydöksistä, ette voi osallistua tutkimukseen.

Merkitkää rasti ruutuun:

☐ Haluan, että minulle kerrotaan, mikäli tutkimuksen aikana aivoistani havaitaan sairauteen viittaavia löydöksiä.

Vakuutan, että minulle on kerrottu tutkimuksesta ja olen lukenut tutkimuspotilaan tiedotteen. Minulle on myös annettu mahdollisuus keskustella kaikista tutkimukseen liittyvistä asioista tutkimushenkilöstön kanssa. Kerättyä aineistoa tullaan käyttämään tieteellisessä raportoinnissa siten, että henkilöllisyyttäni ei voida tunnistaa niistä.

Suostun osallistumaan tutkimukseen ja teen sen vapaaehtoisesti. Olen myös valmis seuraamaan vastaavan tutkijan ja tutkimushenkilöstön minulle antamia ohjeita ennen tutkimusta ja tutkimuksen aikana. Jos en noudata näitä ohjeita, voi vastaava tutkija keskeyttää tutkimuksen minun osaltani. Minulla on oikeus peruuttaa suostumukseni tutkimukseen osallistumisesta ja tutkimuksessa kerättävän aineiston käytöstä tieteellisessä raportoinnissa.

Olen myös tietoinen että voin keskeyttää osallistumiseni tähän tutkimukseen koska tahansa syytä ilmoittamatta ilman, että se vaikuttaa minuun mitenkään. Olen myös tietoinen siitä, että voin peruuttaa suostumukseni, jolloin suostumuksen peruuttamisen jälkeen tietojani ei käytetä enää tutkimustarkoituksessa. Tutkimustietokantaan tallennettuja tietoja ei kuitenkaan voida poistaa tutkimuksesta, jos tiedot on jo ehditty analysoida.

Helsingissä / 20___

_____

Tutkittavan allekirjoitus

_____

Suostumuksen vastaanottajan allekirjoitus

Appendix 3: Manual Muscle Test

Overview:

Manual muscle testing is a manual procedure assessing joint motions. It is a well-known and frequently used method among physiotherapists to diagnose and assess movement impairments. The focus of manual muscle testing is the impairment of the muscles, rather than the amount of strength the muscles possess to perform functional movements and tasks. The limb muscles are categorized by each nerve root distribution.

Grading Scale 0-5: Zero/No Activity (0), Trace Activity (1), Poor (2), Fair (3), Good (4), Normal (5). + and – can be added at each score level based on the examiner.

Phases of Testing: The Break Test, Active Resistance Test, Application of Resistance.

Reference:

Hislop, H. J., & Montgomery, J. (2014). Daniels and Worthingham's muscle testing: techniques of manual examination (9th Ed.). St. Louis, Mo: Saunders / Elsevier. 1-16.

MANUAL MUSCLE TESTING

Name / code _____

Measurer _____ date _____

RIGHT		**LEFT**
TORSO		
_____	Body flexion, coughing and pushing rib cage downwards	_____
SCAPULA		
_____	abduction: external rotation, serratus anterior	_____
_____	elevation: trapezius, pars cran., levator scapulae	_____
_____	adduction: trapezius pars medialis	_____
_____	rotation: rhomboideus minor ja major,	_____
SHOULDER		
_____	flexion 0-90°: deltoideus pars vent.	_____
_____	extension: deltoideus post, latissimus dorsi, teres major	_____
_____	abduction 0-90°: deltoideus pars lat., supraspinatus	_____
_____	horizontal abduction: deltoideus pars post.,	_____
_____	horizontal adduction: pectoralis major,	_____
_____	external rotation: infraspinatus, teres minor	_____
_____	Iiternal rotation: subscapularis, pectoralis major, latisismus dorsi, teres major	_____
ELBOW		
_____	flexion: biceps brachii, brachialis, brachioradialis	_____
_____	extension: triceps brachii	_____

FOREARM

supination: supinator longus, biceps brachii

pronation: pronator teres, pronator quadratus

WRIST

flexion: flexor carpi radialis

flexor carpi ulnaris

extension: extensor carpi radialis

extensor carpi ulnaris

FINGERS

PIP II-V flexor digit. superficialis

DIP II-III flexor digit. profundus I-II

DIP IV-V flexor digit. profundus IV-V

extension MP II-V: extensor digitorum

extensor digiti minimi

extensor indicis

abduction II-V: interossei dorsalis

abductor digiti minimi

adductio II-V: interossei palmares

THUMB

flexino MP: flexor pollicis brevis

IP flexor pollicis longus

extension MP: extensor pollicis brevis

IP extensor pollicis longus

abduction: abductor pollicis brevis

abductor pollicis longus

adduction: adductor pollicis

opposition thumb: opponens pollicis

V-finger opponens digiti minimi

HIP

flexion: iliopsoas

extension: gluteus maximus

abduction: gluteus medius

adduction: adductor magnus

KNEE

flexion: biceps femoris, semitendinosus, semimembranosus

extension: quadriceps femoris

ANKLE

plantar flexion: gastrocnemius, soleus

dorsal flexion and inversion: tibialis anterior

inversion: tibialis posterior

eversion: peroneus longus, peroneus brevis

TOES

flexion MP ja DIP

MP flexor hallucis brevis

DIP flexor digitorum longus

PIP flexor digitorum brevis

IP flexor hallucis longus

extension DIP: extensor digitorum longus, extensor digitorum brevis

extensor hallucis longus

Appendix 4: ASIA

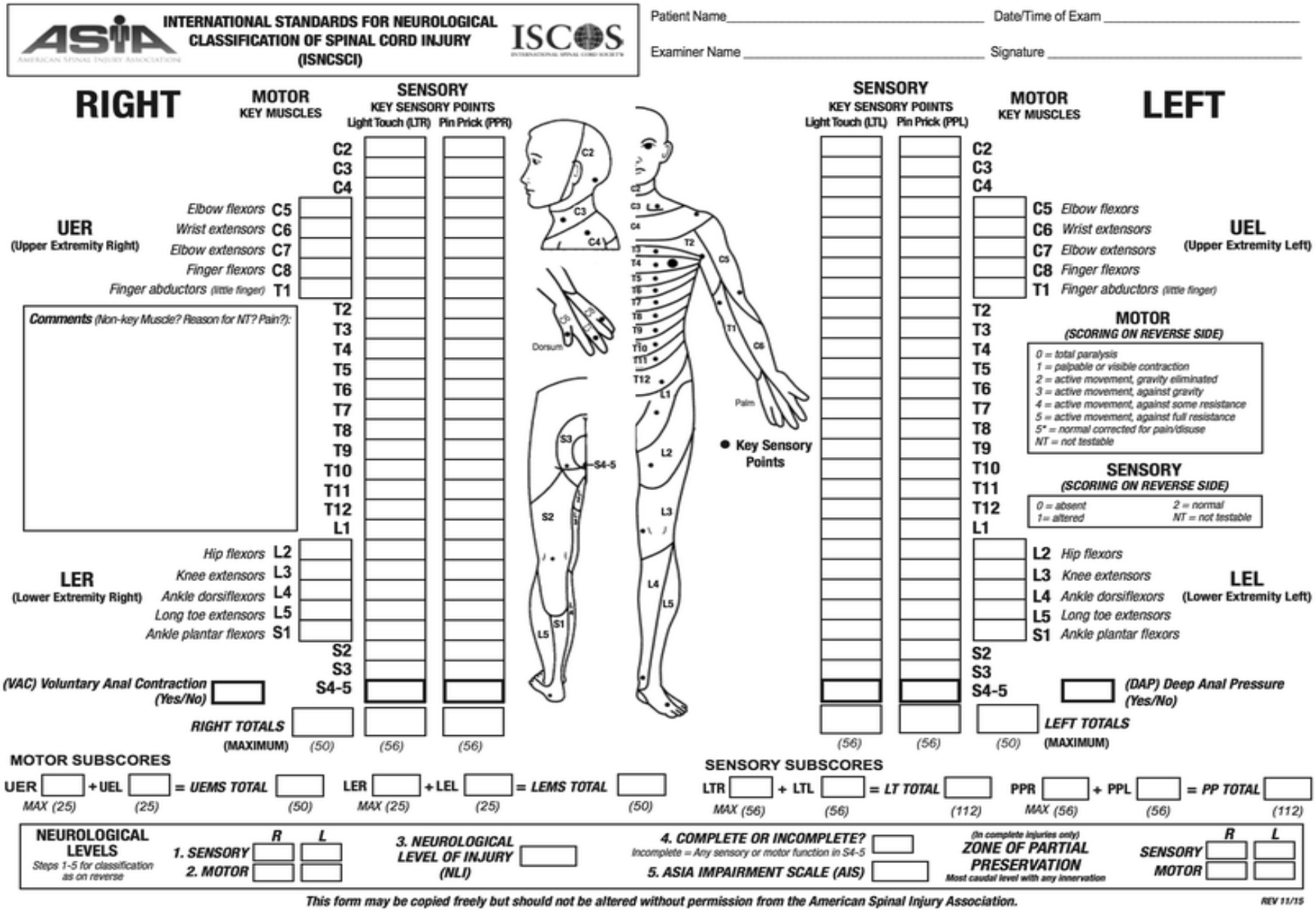
Overview:

The ASIA is an assessment protocol to describe the functional impairment of an individual due to SCI. The full test consists of 1 sensory examination divided into sections based on the 28 dermatomes, 1 motor examination based on myotomes, and 1 anorectal examination. The full examination results are used to define the NLI, the AIS grade of injury classification, as well as the completeness of injury (Hospital 2011, 256). The sensory examination assesses differential response to light touch and pin prick for spinal cord levels C2-T2 on a scale of 0 to 5.

Reference:

Hospital C. (2011). ASIA Impairment Scale. In: Kreutzer, J.S., DeLuca, J., Caplan, B. (eds) Encyclopedia of Clinical Neuropsychology. Springer, New York, NY. https://doi.org/10.1007/978-0-387-79948-3_1792

Appendix 5: SCIM



Overview:

The spinal cord independence measure (SCIM) is a disability scale designed specifically for spinal cord injury individuals. Categories include self-care, respiration, sphincter management, and mobility. The total score ranks on a scale of 0 to 100, with each of the listed categories having different scale ranges depending on the proportional weight the category has on general daily living. For example, respiration and sphincter management ranks 0 to 40, whereas self-care ranks 0 to 20. (Panuccio et al. 2021)

Reference:

Panuccio, F., Grieco, G., D'Angelo, M., & Marquez, M. A. (2021). Measuring Activity of Daily Living in Spinal Cord Injury. In Measuring Spinal Cord Injury (pp. 77–106). essay, Springer.

שירותי בריאות כללית

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Department IV, Medical Director: Dr. Amiram Catz **Tel: 972-9-7709090 Fax: 972-9-7709986** e-mail: amiramc@clalit.org.il

Patient Name: _____ **ID:**_____ **Examiner Name:** _____
(Enter the score for each function in the adjacent square, below the date. The form may be used for up to 6 examinations.)

SCIM-SPINAL CORD INDEPENDENCE MEASURE

Version III, Sept 14, 2002

EXam 1 2 3 4 5 6
DATE \ \ \ \ \ \

Self-Care

1. Feeding (cutting, opening containers, pouring, bringing food to mouth, holding cup with fluid)
0. Needs parenteral, gastrostomy, or fully assisted oral feeding
1. Needs partial assistance for eating and/or drinking, or for wearing adaptive devices
2. Eats independently; needs adaptive devices or assistance only for cutting food and/or pouring and/or opening containers
3. Eats and drinks independently; does not require assistance or adaptive devices

2. Bathing (soaping, washing, drying body and head, manipulating water tap). **A-upper body; B-lower body**

A. 0. Requires total assistance
1. Requires partial assistance
2. Washes independently with adaptive devices or in a specific setting (e.g., bars, chair)
3. Washes independently; does not require **a**daptive **d**evices or **s**pecific **s**etting (not customary for healthy people) (adss)

B. 0. Requires total assistance
1. Requires partial assistance
2. Washes independently with **a**daptive **d**evices or in a **s**pecific **s**etting (adss)
3. Washes independently; does not require **a**daptive **d**evices (adss) or **s**pecific **s**etting

3. Dressing (clothes, shoes, permanent orthoses: dressing, wearing, undressing). **A-upper body; B-lower body**

A. 0. Requires total assistance
1. Requires partial assistance with **c**lothes **w**ith**o**ut **b**uttons, **z**ippers or **l**aces (cwobzl)
2. Independent with cwobzl; requires **a**daptive **d**evices and/or **s**pecific **s**ettings (adss)
3. Independent with cwobzl; does not require adss; needs assistance or adss only for bzl
4. Dresses (any cloth) independently; does not require adaptive devices or specific setting

B. 0. Requires total assistance
1. Requires partial assistancewith **c**lothes **w**ith**o**ut **b**uttons, **z**ipps or **l**aces (cwobzl)
2. Independent with cwobzl; requires adaptive devices and/or specific settings (adss)
3. Independent with cwobzl without adss; needs assistance or adss only for bzl
4. Dresses (any cloth) independently; does not require adaptive devices or specific setting

4. Grooming (washing hands and face, brushing teeth, combing hair, shaving, applying makeup)
0. Requires total assistance
1. Requires partial assistance
2. Grooms independently with adaptive devices
3. Grooms independently without adaptive devices

SUBTOTAL (0-20)

Respiration and Sphincter Management

5. Respiration
0. Requires tracheal tube (TT) and permanent or intermittent assisted ventilation (IAV)
2. Breathes independently with TT; requires oxygen, much assistance in coughing or TT management
4. Breathes independently with TT; requires little assistance in coughing or TT management
6. Breathes independently without TT; requires oxygen, much assistance in coughing, a mask (e.g., peep) or IAV (bipap)
8. Breathes independently without TT; requires little assistance or stimulation for coughing
10. Breathes independently without assistance or device

6. Sphincter Management - Bladder
0. Indwelling catheter
3. Residual urine volume (RUV) > 100cc; no regular catheterization or assisted intermittent catheterization
6. RUV < 100cc or intermittent self-catheterization; needs assistance for applying drainage instrument
9. Intermittent self-catheterization; uses external drainage instrument; does not need assistance for applying
11. Intermittent self-catheterization; continent between catheterizations; does not use external drainage instrument
13. RUV <100cc; needs only external urine drainage; no assistance is required for drainage
15. RUV <100cc; continent; does not use external drainage instrument

7. Sphincter Management - Bowel
0. Irregular timing or very low frequency (less than once in 3 days) of bowel movements
5. Regular timing, but requires assistance (e.g., for applying suppository); rare accidents (less than twice a month)
8. Regular bowel movements, without assistance; rare accidents (less than twice a month)
10. Regular bowel movements, without assistance; no accidents

8. Use of Toilet (perineal hygiene, adjustment of clothes before/after, use of napkins or diapers).
0. Requires total assistance
1. Requires partial assistance; does not clean self
2. Requires partial assistance; cleans self independently
4. Uses toilet independently in all tasks but needs adaptive devices or special setting (e.g., bars)
5. Uses toilet independently; does not require adaptive devices or special setting)

SUBTOTAL (0-40)

Mobility (room and toilet)

DATE \ \ \ \ \ \ \

9. Mobility in Bed and Action to Prevent Pressure Sores

0. Needs assistance in all activities: turning upper body in bed, turning lower body in bed, sitting up in bed, doing push-ups in wheelchair, with or without adaptive devices, but not with electric aids
2. Performs one of the activities without assistance
4. Performs two or three of the activities without assistance
6. Performs all the bed mobility and pressure release activities independently

10. Transfers: bed-wheelchair (locking wheelchair, lifting footrests, removing and adjusting arm rests, transferring, lifting feet).

0. Requires total assistance
1. Needs partial assistance and/or supervision, and/or adaptive devices (e.g., sliding board)
2. Independent (or does not require wheelchair)

11. Transfers: wheelchair-toilet-tub (if uses toilet wheelchair: transfers to and from; if uses regular wheelchair: locking wheelchair, lifting footrests, removing and adjusting armrests, transferring, lifting feet)

0. Requires total assistance
1. Needs partial assistance and/or supervision, and/or adaptive devices (e.g., grab-bars)
2. Independent (or does not require wheelchair)

Mobility (indoors and outdoors, on even surface)

12. Mobility Indoors

0. Requires total assistance
1. Needs electric wheelchair or partial assistance to operate manual wheelchair
2. Moves independently in manual wheelchair
3. Requires supervision while walking (with or without devices)
4. Walks with a walking frame or crutches (swing)
5. Walks with crutches or two canes (reciprocal walking)
6. Walks with one cane
7. Needs leg orthosis only
8. Walks without walking aids

13. Mobility for Moderate Distances (10-100 meters)

0. Requires total assistance
1. Needs electric wheelchair or partial assistance to operate manual wheelchair
2. Moves independently in manual wheelchair
3. Requires supervision while walking (with or without devices)
4. Walks with a walking frame or crutches (swing)
5. Walks with crutches or two canes (reciprocal walking)
6. Walks with one cane
7. Needs leg orthosis only
8. Walks without walking aids

14. Mobility Outdoors (more than 100 meters)

0. Requires total assistance
1. Needs electric wheelchair or partial assistance to operate manual wheelchair
2. Moves independently in manual wheelchair
3. Requires supervision while walking (with or without devices)
4. Walks with a walking frame or crutches (swing)
5. Walks with crutches or two canes (reciprocal waking)
6. Walks with one cane
7. Needs leg orthosis only
8. Walks without walking aids

15. Stair Management

0. Unable to ascend or descend stairs
1. Ascends and descends at least 3 steps with support or supervision of another person
2. Ascends and descends at least 3 steps with support of handrail and/or crutch or cane
3. Ascends and descends at least 3 steps without any support or supervision

16. Transfers: wheelchair-car (approaching car, locking wheelchair, removing arm- and footrests, transferring to and from car, bringing wheelchair into and out of car)

0. Requires total assistance
1. Needs partial assistance and/or supervision and/or adaptive devices
2. Transfers independent; does not require adaptive devices (or does not require wheelchair)

17. Transfers: ground-wheelchair

0. Requires assistance
1. Transfers independent with or without adaptive devices (or does not require wheelchair)

SUBTOTAL (0-40)

TOTAL SCIM SCORE (0-100)

Appendix 6: Hand Function Tests

Overview:

The Box and Block test measures unilateral gross manual dexterity. The individual must transfer blocks of the same shape and size one at a time across a partition and drop them on the opposite side. The individual has 60 seconds to transfer as many blocks as possible. (Desrosiers et al. 1994).

The Nine Hole Peg test is designed to assess finger dexterity. In the standard test, individuals must place small cylindric pegs into holes on a peg board, then remove them all after all holes have been filled. SCI modification: test is timed for 60 seconds to place as many pegs as possible. (Backman et al. 1992)

Grip strength tests were performed with a standardized Jamar Plus+ digital dynamometer. Grip width was positioned at the standard position of 3 for males. The individual must have the elbow flexed to 90 degrees (or as close as possible), with the arm positioned to their side. The individual has 3 attempts, and the highest strength is recorded. (Ewing 1992). Finger pinch tests—index and thumb pinch, key pinch, and a three-finger pinch—were performed with a pinch gauge. The sitting position is the same as the grip strength test. The individual has 2 attempts with 30 seconds in between, starting with the dominant hand. (Stegink et al. 2003)

References:

Backman C, Cork S, Gibson D. Parsons J. Assessment of hand function: The relationship between pegboard dexterity and applied dexterity. Can J Occup Ther 1992;59:209. https://doi.org/10.1177/000841749205900406

Desrosiers, J., Bravo, G., Hébert, R., Dutil, E., & Mercier, L. (1994). Validation of the Box and Block Test as a measure of dexterity of elderly people: reliability, validity, and norms studies. Archives of physical medicine and rehabilitation, 75(7), 751–755.

Ewing E. Grip strenght. Clinical assessment recommendations. 2nd ed. Chicago; American Society of Hand Therapists, 1992.

Name / code

Assessor _____ date _____

Box and block

Hand dominance: right/left

Results:	right	units	left	units

9hole-Peg

Results:	right	units	left	units
Time:				

Grip strentgh	Grasp level	3 is male		
Results:	right	Kg	left	kg

Index finger and thumb pinch

Results:	right	kg	left	kg

Key pinch

Results:	right	kg	left	kg

Three finger pinch

Results:	right	kg	left	kg

Appendix 7: Activities of Daily Living

Overview: Subjective assessment of hand function in activities of daily living using functional tasks. These included kitchen related activities (for example cutting bread), dressing related activities (buttoning a shirt), work/home related activities (writing with a pencil). These tasked were recorded on a tablet.

Testing hand functions in daily activities. Patient can / can't independently manage the task. Task will be filmed. The maximum time to perform the task is 60 seconds.

Patient code: _____ date: _____

Hand dominance: right _____ left _____

Function	Right: yes / no	Time used	Left: yes / no	Time used
Spoon used				
Cutting bread with a knife (bread is 0,5 l bottle)				
Opening the bottle, spiral cap (0,5 l bottle)				
Pouring water in glass from a bottle				
Drinking from the glass				
Reaching an object (empty 0.5 l bottle) from diagonal upfront (135° arm)				
Buttoning and unbuttoning (3 buttons)			Two hand work	
Pencil grip and drawing a triangle				
Pad or tablet use and writing a name (Sanna Suomalainen). Tablet is lying on the table.				
Opening a lock (wc door)				

Appendix 8: Modified Ashworth Scale

Overview:

This test involves a physiotherapist who manually moves each joint through a passive full range of motion. They rate the perceived level of resistance of the limb during the motion. The scale of the test ranges from 0-4, with 0 = no increase in muscle tone and 4 = limb rigid in flexion or extension. (Dunning 2011, 254). Physiotherapist can decide to include a 1+ score between 1 and 2.

Reference:

Dunning, K. (2011). Ashworth Spasticity Scale (and Modified Version). In: Kreutzer, J.S., DeLuca, J., Caplan, B. (eds) Encyclopedia of Clinical Neuropsychology. Springer, New York, NY. https://doi.org/10.1007/978-0-387-79948-3_1792

MAS, Modified Ashworth Scale

Scoring

0 = Normal tonus, tonus doesn't increase with movement

1 = Slight resistance to passive movement at the end of trajectory

1+ = Slight resistance to passive movement at the end of trajectory, when less than half of the trajectory is left.

2 = Resistance increases during almost the whole trajectory, but part of the extremity is easily moveable.

3 = Notable increase of the resistance, passive movement is hard.

4 = Strong resistance towards passive movement, passive movement almost impossible.

Spastic muscles	Right	Left
Elbow extensors		
Elbow flexors		
Wrist extensors		
Wrist flexors		
Finger extensors		
Finger flexors		
Thumb extensors		
Thumb flexors		

Appendix 9: Pain Questionnaire

Overview: The pain questionnaire used what from the International Spinal Cord Injury Pain Basic Data Set, version 3.0. This evaluation is an accessible and standardized method to assess specific pain complications as well as multiple pain problems. Pain is defined as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage" (Raja et al. 2020). If pain is present, there are 3 interference factors to further understand the pain's effect on daily activities, mood, and sleep. These rank on a scale of 0-10. Finally, location and type of pain are assessed.

Reference:

INTERNATIONAL SPINAL CORD INJURY DATA SETS (asia-spinalinjury.org)

Raja SN, Carr DB, Cohen M, Finnerup NB, Flor H, Gibson S, Keefe FJ, Mogil JS, Ringkamp M, Sluka KA, Song XJ, Stevens B, Sullivan MD, Tutelman PR, Ushida T, Vader K. The revised International Association for the Study of Pain definition of pain: concepts, challenges, and compromises. Pain. 2020;161(9):1976-1982.

PAIN (upper)
Patient code: _____ Date: _____ Measurer: _____

1. Have you had pain during the last seven days, including today?

   _____ (0 no, 1 yes)

2. How many separate pain issues do you have?

   _____ (scale 0-5) (If pain issue is over 5, mark the real number, but coefficient number used is still 5)

3. Usually, how much does the pain bother your daily activities last week?

   _____ (scale 0-10)

4. Usually, how much does the pain bother your usual mood last week?

   _____ (scale 0-10)

5. Usually, how much does the pain bother your abilities to get good night sleep?

   _____ (scale 0-10)

Subpoint 0-36

PAIN PLACES		Right	Left
Upper extremity	shoulder		
	arm		
	elbow		
	forearm		
	wrist		
	hand/fingers		
Other, what:			

PAIN TYPE		
Nociceptic pain	Musculoskeletal pain	
Visceral pain	Internal organ pain	
	Other	
Neuropathic pain	SCI level region	
	Lower than the level of SCI	
	Other neuropathic pain (such as trigeminus neuralgia, or ghost pain lower than the level of SCI)	

Magnitude of pain
_____ 0 no pain – 10 pain as hard as you can imagine

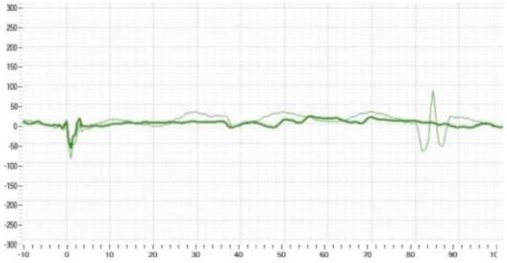
Do you use or have you had treatment for your pain issue:
_____ 0 no 1 yes. What: _____

Appendix 10: MEP Values

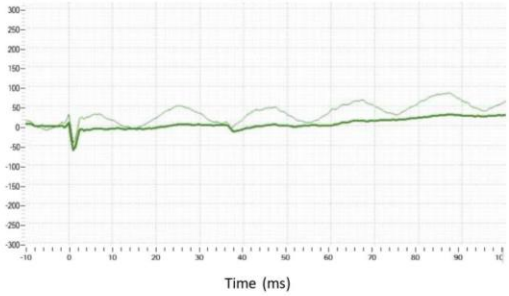
Right Hand MEPs

PRE INTERVENTION

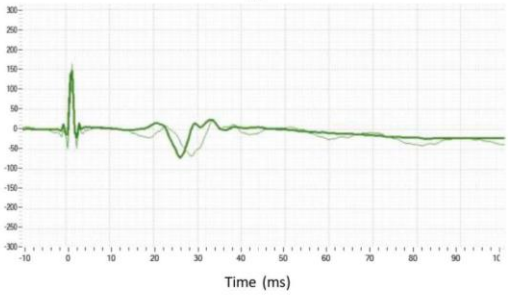
APB



ADM

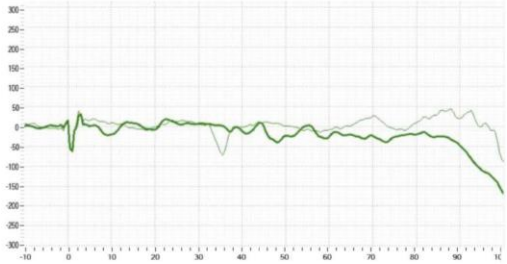


ED

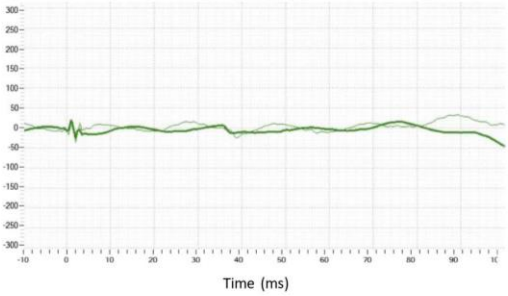


POST INTERVENTION

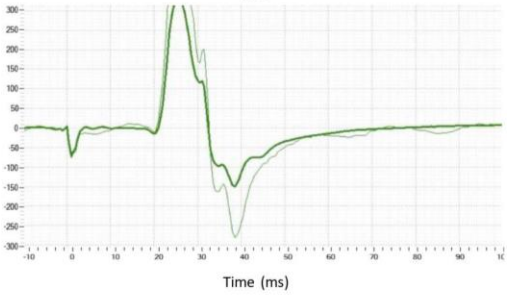
APB



ADM



ED

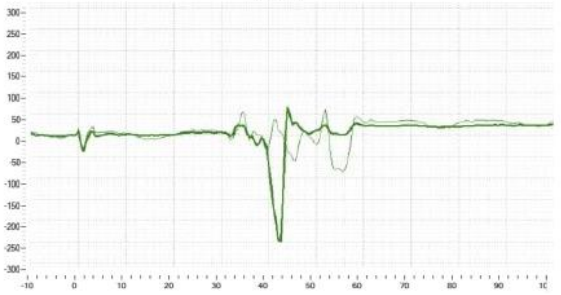


Left Hand MEPs

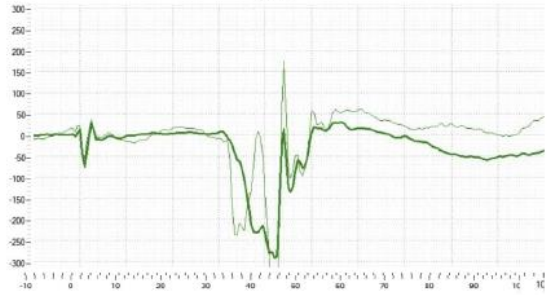
PRE INTERVENTION

POST INTERVENTION

APB



APB



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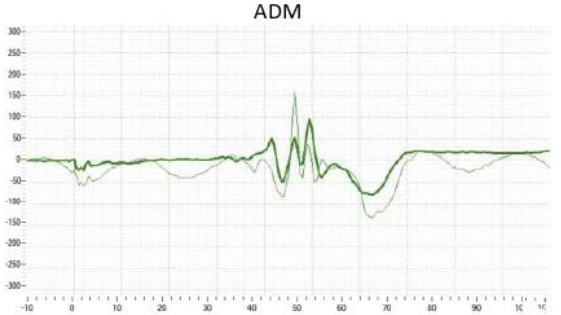

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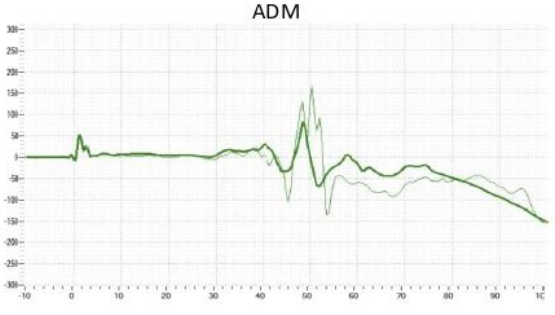
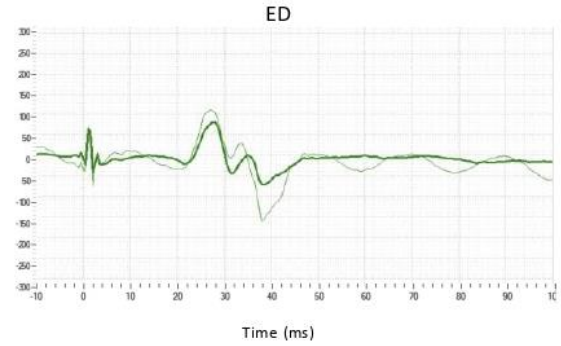


ED



ED