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# Exploring the Effect of Combining Repetitive Transcranial Magnetic Stimulation with Functional Electrical Stimulation Cycling on Lower Extremity Function Following Incomplete Spinal Cord Injury

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A thesis submitted in partial fulfillment of the requirements for the Master of Science degree in Health and Rehabilitation Sciences

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## Abstract

Spinal cord injury (SCI) is a neurological condition that disrupts lower extremity function, limiting mobility and independence. This dissertation explores the feasibility, acceptability, and safety of combining repetitive transcranial magnetic stimulation (rTMS) with functional electrical stimulation (FES) cycling to improve lower extremity function following motor incomplete SCI (iSCI). This study is a case series pilot study in which participants with iSCI underwent a combined protocol of rTMS and FES cycling for six weeks. The results demonstrate the preliminary feasibility, participant acceptability, and safety of combining rTMS and FES cycling. While results varied between participants, one participant showed improvements in walking speed, muscle strength, and functional tests. These findings suggest the potential of pairing rTMS with FES cycling to improve lower extremity function following iSCI. Further studies with larger sample sizes are warranted to confirm efficacy.

## Keywords

Incomplete spinal cord injury (iSCI), lower extremity function, repetitive transcranial magnetic stimulation (rTMS), functional electrical stimulation (FES) cycling, gait velocity, muscle strength, Timed-Up-and-Go (TUG), Sit-to-Stand (STS), postural sway, Lower Extremity Motor Score (LEMS), Walking Index for Spinal Cord Injury (WISCI) II, feasibility, acceptability, safety

## Summary for Lay Audience

Spinal Cord Injury (SCI) is a serious condition that happens when the spinal cord is damaged, often due to accidents, falls, violence, or tumours. This damage can cause problems like losing the ability to move your legs, walk, keep balance, and have strong muscles. Helping people with SCI regain their independence to do daily activities, like walking, is very important.

This study looked at a new way to help people with SCI using two techniques: repetitive transcranial magnetic stimulation (rTMS) and functional electrical stimulation (FES) cycling. rTMS uses magnetic pulses to stimulate the part of the brain that controls movement, while FES uses mild electrical currents to activate leg muscles, helping people pedal a bike.

We wanted to see if combining these techniques could improve leg function in people with incomplete SCI (iSCI). Three participants took part in the study. They were split into two groups: one group received real rTMS with FES cycling, and the other group received a fake (sham) rTMS with FES cycling over six weeks. We checked their leg function four times during the study to see if there were any improvements in walking speed, balance, and muscle strength.

All participants found the combined treatment to be tolerable. Additionally, there were no serious adverse events observed. While the results varied for each person, we saw some encouraging improvements, like faster walking speed, better balance, and stronger muscles. However, more research with more participants is needed to confirm these findings.

Even with the differences between individuals, these first results are promising. Combining rTMS and FES cycling might be a helpful way to improve leg function after iSCI. This could lead to better mobility, more independence, and a higher quality of life for people with this condition.

## Acknowledgments

I would like to sincerely express my gratitude to my supervisor, Dr. Janelle Unger, without whom this thesis would not have been possible. Her invaluable guidance, insightful feedback, and unwavering support throughout this project were truly indispensable. I am genuinely fortunate to work with her, and I am very grateful for the opportunity I have been given. Dr. Unger's guidance, not only in research but also in many other aspects, has been the highlight of my experience during this master's degree. I owe many of my accomplishments to Dr. Unger's kindness and her belief in me.

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This project would not have been possible without the help and support of Stephenie Cornell, the rehabilitation coordinator at Parkwood Hospital. She did a tremendous job providing us access to FES bikes and giving us the opportunity to advertise our study to local healthcare professionals on-site. Additionally, I would like to thank Ariel Gavronski for training me on how to use FES bikes. She was always very flexible with her fitness program and scheduling sessions for the participants.

Moreover, I would like to extend special thanks to Jordan Eggiman-Ketter, the research assistant in this project, who was present in every session with every participant and provided significant assistance in conducting the sessions. I could not have completed this project without her collaboration. I am also extremely thankful for my three participants who committed to participating in this project and making an impact on their community; none of this would have been possible without their attention and time.

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## List of Abbreviations

SCI: Spinal cord injury

iSCI: Incomplete spinal cord injury

rTMS: Repetitive transcranial magnetic stimulation

FES: Functional electrical stimulation

TUG: Timed-Up-and-Go

STS: Sit-to-Stand

LEMS: Lower Extremity Motor Score

WISCI: Walking Index for Spinal Cord Injury

GRC: Global Rating of Change

# Chapter 1: Introduction

This dissertation explores the feasibility and effectiveness of combining two non-invasive neuromodulation techniques, repetitive transcranial magnetic stimulation (rTMS) and functional electrical stimulation (FES) cycling to improve lower extremity function following motor incomplete spinal cord injury (iSCI). This dissertation is a pilot trial which will focus on people with motor incomplete spinal cord injury, and the term iSCI will refer to this condition throughout this dissertation. The following chapter will provide the readers with the required background information to provide a better understanding of the context of this study.

## 1.1 Spinal Cord Injury

The spinal cord is the part of the central nervous system that is responsible for transmitting information from the brain to the periphery and vice versa, however, the spinal cord is also capable of interpreting signals and coordinating movement. For example, the spinal cord responds to sensory information through reflex arcs and can coordinate rhythmic movements such as walking without the involvement of volitional motor commands from the brain through central pattern generators.<sup>1</sup> The spinal cord consists of several spinal tracts that are oriented longitudinally, such as the corticospinal tract. The corticospinal tract originates from the neurons in the primary motor cortex (M1), premotor cortex, and somatosensory cortex in the brain.<sup>2</sup> The corticospinal tract is one of the most important tracts in the human body as it is the primary pathway for transmitting voluntary motor signals. This tract transfers the signals from the brain to the spinal cord level and then synapses with the lower motor neurons and activates muscle contractions.<sup>2</sup> A spinal cord injury (SCI) is defined as damage to the spinal tracts, including the corticospinal tract, that can impair the transmission of motor signals between the brain and other sites of the body depending on the level and severity of the lesion.<sup>3</sup>

### 1.1.1 SCI Epidemiology, Etiology, and Classification

Spinal cord injuries can be classified in various ways including the severity of the injury (complete vs. incomplete), location of the injury (cervical, thoracic, lumbar), mechanism of injury (traumatic vs. non-traumatic), or the resulting condition of the injury (paraplegia or tetraplegia). Paraplegia is characterized by lesions in the thoracic or lumbar spine resulting in paralysis from the trunk down and affecting the lower parts of the body.<sup>4</sup> Tetraplegia is due to an injury in the cervical spinal cord resulting in paralysis in the arms as well as the trunk and legs, with potential head and neck involvement as well.<sup>4</sup> One of the most common ways to classify SCI is based on the American Spinal Injury Association Impairment Scale (AIS), which categorizes injuries as either complete or incomplete based on the presence of sacral sparing. Sacral sparing is defined as the presence of sensory or motor function in the most caudal sacral segments; a complete injury refers to the absence of any sensory and/or motor function in the most caudal sacral segments of the spinal cord (S4-5) and incomplete injury is defined as the presence of some sensory and/or motor function in the S4-5 segments. Grading the levels of impairment based on this scale is described in Table 1.

**Table 1.** AIS Scores Description<sup>3</sup>

<b>Level</b>	<b>Description</b>
A = Complete	No sensory or motor function is preserved in the sacral segments S4-5.
B = Sensory incomplete	Sensory but not motor function is preserved below the neurological level and includes the sacral segments S4-5, AND no motor function is preserved more than three levels below the motor level on either side of the body.
C = Motor incomplete	Motor function is preserved below the neurological level, and more than half of key muscle functions below the single neurological level of injury have a muscle grade of less than 3 (i.e. the person is not able to complete the action against gravity).
D = Motor incomplete	Motor function is preserved below the neurological level, and at least half (half or more) of key muscle functions below the neurological level of injury have a muscle grade of more than 3 (i.e. the person is able to complete the action against gravity and with added resistance).
E = Normal	If sensation and motor function are graded as normal in all segments, and the patient had prior deficits, then the AIS grade is E. Individuals without an SCI do not receive an AIS grade.

Lastly, SCI can be classified into three stages: acute, subacute, and chronic. The acute phase starts from the beginning of the injury and lasts for four months; the period between four months and one year is classified as the subacute phase; and the chronic phase begins after one year post injury.<sup>5</sup> Qualifications of the acute stage include the initial trauma and subsequent changes that happen physiologically and neurologically.<sup>6</sup> The subacute stage is characterized by the body stabilizations and the initial attempts for recovery. During this phase, rehabilitation and preventing secondary complications are vital.<sup>5</sup> Finally, the chronic stage occurs one year post injury and during this phase, the lesion further develops and forms a glial scar.<sup>6</sup> Individuals in the chronic stage experience a plateau in their motor recovery, and the focus of rehabilitation shifts to increasing independence and improving the quality of life despite the injury.<sup>7</sup> This study specifically targets individuals with chronic SCI.

The prevalence of SCI in Canada was estimated to be 85,556 individuals in 2010, with 51% of those being of traumatic cause and 49% of non-traumatic etiology.<sup>8</sup> Of these individuals, 52% have incomplete tetraplegia, 18% have incomplete paraplegia, and the remaining 30% have complete paraplegia or tetraplegia.<sup>9,10</sup> In Canada, the most common traumatic etiology for SCI is a fall, followed by motor vehicle accidents, sports, other causes such as work-related injuries, and assaults. Non-traumatic injuries are most often caused by degenerative diseases, followed by tumours, infection, and other sources such as spinal hematomas, vascular diseases, inflammation, and congenital disorders.<sup>11</sup>

### 1.1.2 Secondary Complications and Functional Impairments Following SCI

Following an injury to the spinal cord, multiple secondary complications can occur such as spasticity, pressure sores, joint overuse, muscle atrophy, and muscle weakness.<sup>12-16</sup> These complications can result from paralysis, disuse, and extreme immobilization, however, the processes that happen in the nervous system after the injury are responsible as well. Post injury type I muscle fibres, which are considered slow and operate oxidatively, change to type II fibres that are fast contracting and glycolytic. As a result of this conversion, there is an atrophy in muscles by nearly 30-60% which is responsible for the fatiguability of the muscles after the injury.<sup>17</sup> In addition to the muscle atrophy, there is a high rate of bone loss following the SCI that is uniquely rapid and localized to the



segments below the lesion.<sup>17,18</sup> It is more likely that the primary reason for bone loss is due to the immobilization after the injury and the following unloading which prevents the creation of new bone cells.<sup>19</sup> These musculoskeletal complications are preventable by early and ongoing rehabilitation. Muscle activation can cause improved muscle strength and reduced bone osteoporosis.<sup>20</sup> Therefore, the importance of rehabilitation in reducing these complications and improving the quality of life, is evident. Neuroplasticity is the main mechanism of recovery after spinal cord injury and will be described in detail in the following section.

## 1.2 Neuroplasticity

Neuroplasticity is defined as the ability of the nervous system to change and modify its function in response to an internal or external stimuli.<sup>21</sup> The process of neuroplasticity is a vital part of recovery after neurological injuries.<sup>21</sup> After an incomplete injury, several mechanisms of plasticity occur which can be enhanced through rehabilitative interventions. Structural plasticity occurs due to changes in the anatomy of circuits such as an increase in the growth of dendrites and axons. Axonal sprouting is a type of this mechanism which refers to the growth of new branches in intact axons; new neuronal pathways are created because of this mechanism.<sup>22</sup> Compensatory plasticity refers to changes in the structure of existing intact pathways to compensate for the lost circuits.<sup>22</sup> Alternatively, functional neuroplasticity is due to changes in the function of the circuits to compensate for the injury; these changes include restoration of the activity in the damaged pathways or increased activity in the intact ones.<sup>23</sup> Synaptic reorganization is an example of this mechanism, and it happens when the strength and number of the synaptic connections change and lead to reformation of neuronal circuits.<sup>24</sup>

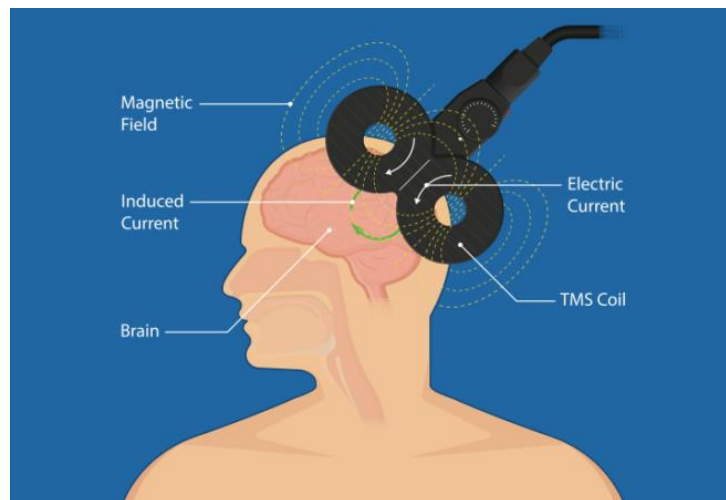
Although neuroplasticity is the main mechanism of recovery following injury, it can lead to negative changes as well. The negative effect of plasticity is especially present in individuals who are inactive, due to maladaptive use of afferent inputs and the loss of efferent inputs, which leads to deterioration of the normal pathways.<sup>25</sup> Some negative adaptations result from abnormal sprouting of axons in an attempt to compensate for the lost connections and the process of regeneration in response to inflammation. These new connections lead to hyperexcitability of the pathways and create inefficient circuits.

However, the same processes can lead to various positive changes in the central nervous system (CNS) if harnessed correctly; new connections created because of sprouting can re-establish the lost pathways and restore lost functions.<sup>26</sup> Consequently, rehabilitation plays a vital role in guiding plasticity to create effective and useful connections in the nervous system. It has been shown that the process of plasticity is dependent on afferent impulses; in other words, signals from receptors in skin, joints, and muscles can help the nervous system to effectively reshape the neuronal connections.<sup>27</sup> The process of neuroplasticity is also influenced by the efferent impulses from the brain to lower neural pathways. In other words, neuroplasticity is highly dependent on the activity level in the specific pathway; the more the neural pathway is fired the more synaptic connections are made and the more growth that can occur along the axons.<sup>28</sup> Overall, neuroplasticity is an important mechanism of recovery after damage to the nervous system and understanding ways to enhance this natural process can benefit people with SCI in their motor recovery greatly. One of the methods of inducing neuroplasticity is by using rTMS; this method is explained in the subsequent section in detail.

### 1.3 Repetitive Transcranial Magnetic Stimulation (rTMS)

Four decades ago, two scientists discovered a method of stimulating the brain non-invasively through the intact scalp, transcranial electrical stimulation (TES).<sup>29,30</sup> This machine was able to stimulate certain areas of the brain and produce a motor-evoked potential (MEP) in the muscles. An MEP is an electrical signal recorded from a muscle in response to electrical or magnetic stimulation of the cortex.<sup>31</sup> The downside of using TES was that it was painful because it also activates the fibres associated with pain perception in the scalp.<sup>29,30</sup> To solve this problem, another method was created that could have the same effect on the brain with little or no pain; transcranial magnetic stimulation (TMS) is a non-invasive method to stimulate neural pathways focally through the skull. TMS functions based on Faraday's law of physics; it consists of a coil that is placed over the scalp, and when a strong electrical current passes through the coil, a magnetic field is produced that reaches the brain.<sup>32</sup> Figure 1 illustrates the magnetic and electrical fields produced in the brain because of the TMS pulses. TMS can be used in three different forms, single pulse which delivers a single stimulus to a specific area of the brain and is

mainly used for assessment of corticospinal excitability<sup>33</sup>, paired pulse which translates as delivering two sequential TMS pulses with a short inter-pulse interval<sup>34</sup> and is used to study the excitatory and inhibitory interactions between various brain regions<sup>35</sup>, and repetitive TMS (rTMS) which delivers multiple pulses in a row over a short time period.<sup>33</sup> The latter, rTMS, has been shown to have long-lasting, persistent effects on cortical excitability, meaning it can be used as an intervention.<sup>36</sup> If rTMS is used in a high-frequency setting (>5Hz) it can increase cortical excitability shown by the increased amplitude of MEPs<sup>37,38</sup> and if it is used in a low-frequency setting (<1Hz) it reduces the corticomotor excitability which is shown by the reduced size of the MEPs.<sup>37,39</sup> Therefore, high-frequency rTMS is thought to be excitatory and low-frequency rTMS is inhibitory. rTMS is capable of enhancing neuroplasticity by causing long-term potentiation (LTP), or strengthening of the neural synapses through an increased number of transmitted signals between two neurons.<sup>40</sup> Furthermore, LTP can be induced by a short-term high-frequency presynaptic activity.<sup>41</sup> This means that the use of rTMS can increase the LTP in the presynaptic neuron and enhance motor function.<sup>42</sup> Also, according to previous literature, it has been shown that rTMS can reduce corticospinal inhibition and therefore improve the recovery of motor function after damage to the nervous system.<sup>43,44</sup>



**Figure 1.** Magnetic and electrical currents produced in the brain because of TMS pulses. (Image source: Sapien Labs. URL: <https://sapienlabs.org/mentallog/the-basics-of-transcranial-magnetic-stimulation/>)

### 1.3.1 rTMS Effects in SCI

As mentioned in the previous section, rTMS can be used to enhance excitability in excitatory pathways and reduce inhibition, therefore improving motor function. Various studies have investigated the effect of high-frequency rTMS on function in individuals with SCI. rTMS was used in a study by Belci et al with the aim of improving upper extremity function in people with chronic iSCI. Stimulation was applied to M1 in the brain and participants went through 5 sessions of sham rTMS followed by 5 sessions of active stimulation. The results of this trial showed improvements in functional tests of the upper extremity such as the 9-hole peg test and AIS assessments revealed improvements in both sensory and motor functions.<sup>44</sup> In a similar study by Kuppuswamy et al, it was shown that after the use of rTMS over M1, the active motor threshold (AMT) was increased in first dorsal interosseus muscles, indicating improvement of corticospinal excitability and function.<sup>45</sup> In another study, Wincek et al evaluated the long-term effects of combining rTMS with supervised physiotherapy exercises for individuals with iSCI. The results showed that spasticity was decreased in the upper extremity after using these interventions and an increase in the transmission of efferent impulses was observed based on the data obtained from MEP recordings.<sup>46</sup> The effect of rTMS in the lower extremity following iSCI was assessed in a randomized double-blind study by Benito et al. In this study, 17 participants were randomized to undergo either active or sham rTMS during 15 sessions of therapy over a period of three weeks. All participants received the standard treatment which included training of activities of daily living, occupational therapy for upper extremities, fitness, sports, hydrotherapy, and gait training. rTMS intervention was scheduled just before the gait training to enhance the effects. Outcome measures of this study include Lower Extremity Motor Score (LEMS), modified Ashworth Scale (MAS), Walking Index for Spinal Cord Injury (WISCI) II, 10-Meter Walking Test (10MWT), Timed-Up-and-Go (TUG) test, and gait parameters including step length and cadence. Results of the trial showed significant improvements in LEMS, MAS, and TUG scores in the active group as opposed to the sham group as well as improved gait parameters such as velocity, cadence, and step length. The authors also concluded that these effects were maintained for at least two weeks after the last session.<sup>47</sup> In another study, Kumru et al combined the use of rTMS with Lokomat gait training in people with iSCI. In this study,

31 participants were randomized to receive either sham or active rTMS during a 20-session daily protocol and were evaluated for several outcomes such as spasticity by the MAS scale, muscle strength by LEMS and upper extremity motor score (UEMS) and walking ability by 10MWT and WISCI-II scale. The results of this study showed that motor improvements in both the upper and lower extremities were significantly greater in the active group compared to the sham group. Moreover, more participants in the active group showed improvements in performing 10MWT compared to the sham group, likely due to increased activation in supraspinal centers related to gait, facilitation of corticospinal excitability, and reduction in corticospinal inhibition.<sup>48</sup> QuadroPulse rTMS is a modern form of rTMS which consists of trains of four pulses that are delivered with an ultra-high frequency (2ms inter-pulse interval) with an inter-train interval of more than 5 seconds. This form of rTMS has also been shown to improve the function of the upper and lower extremities following iSCI. This effect is associated with increased cortical excitability measured from baseline to follow-up visits.<sup>49</sup> In a study done by Alexeeva et al, a 5-session QuadroPulse rTMS was used in addition to exercise therapy which led to increased walking speed without any adverse effects.<sup>49</sup> Overall, previous literature demonstrates the promising effect of using rTMS to enhance upper and lower extremity motor function following iSCI.

## 1.4 Functional Electrical Stimulation (FES)

Over 2000 years ago, the first trials to treat a paretic muscle using electricity were conducted.<sup>50</sup> Static electricity was used by Kratzenstein in 1744 to treat contracture of the fingers;<sup>51</sup> later in the 19<sup>th</sup> century, electrical stimulation was applied to muscles using surface electrodes to reduce spasticity by Duchenne.<sup>52</sup> In 1951, Giaimo used electrical stimulation in the form of ‘faradic current’<sup>51</sup> and attempts to use electrical current followed by Wladimir T. Liberson who utilized electricity in the form today known as neuromuscular electrical stimulation (NMES) to treat upper motor neuron deficits.<sup>53</sup> Throughout recent years this technology has been improved to transistorized, portable stimulators used to treat various orthopedic and neurological disorders. NMES operates by stimulating the peripheral neurons and prompting them to produce a response by increasing cell excitability. One of the most common applications of electrical currents is

in neurological rehabilitation, where it is used to help paralyzed or weak but still innervated muscles produce movement. Functional electrical stimulation (FES) is a type of NMES that specifically uses electrical stimulation during functional movements to augment the effects. Functional movements that are facilitated by FES may include reaching, grasping, walking, or cycling.<sup>54</sup>

An FES device usually consists of an electrical stimulator and stimulation electrodes. The stimulator is responsible for producing electrical discharges that can elicit a response in the neurons. Each stimulator consists of one or more channels each with two electrodes: cathode and anode. The electrical discharges are delivered to the muscles through the electrodes. Electrodes can be implanted, which are placed inside the muscle, or they can be surface electrodes which are simply placed on the skin of the muscle of interest to facilitate a non-invasive approach.<sup>55</sup>

Electrical pulses have several characteristics that play a vital role in the current's final effect; these characteristics include stimulation intensity, stimulation frequency, and pulse shape (Fig 2).<sup>55</sup> Each of these parameters is described briefly below.

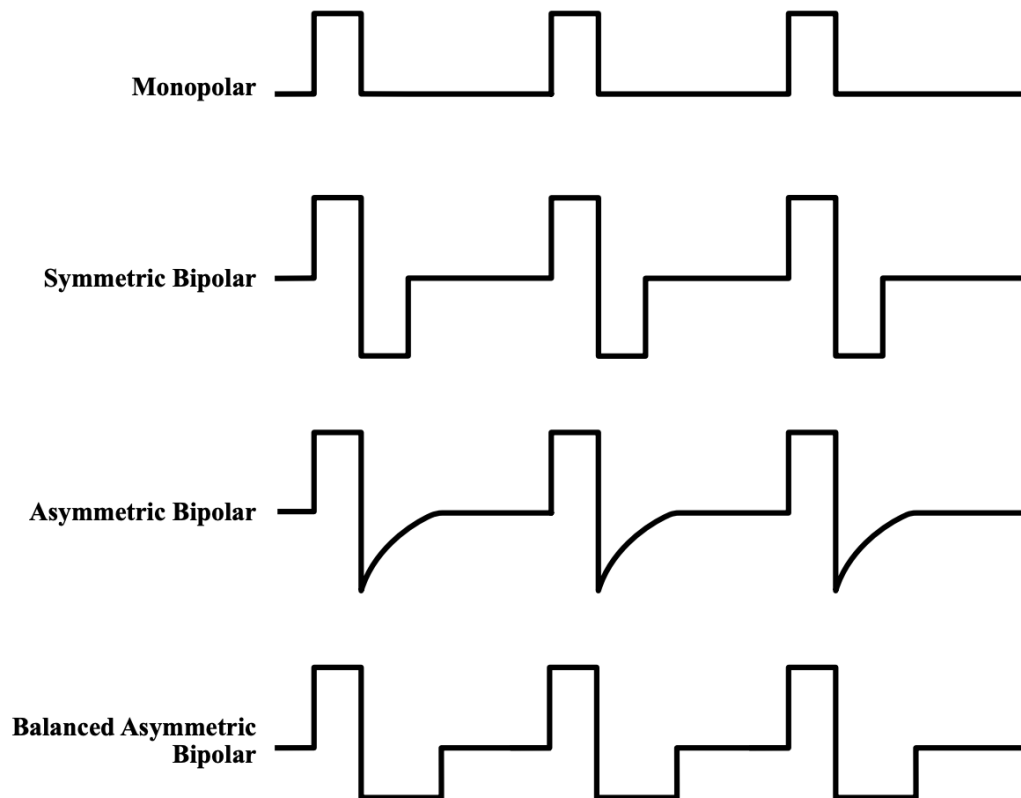
**Intensity:** Intensity is determined by different parameters. Amplitude is the magnitude of the pulse, which plays a role in the type of nerve fibre that is stimulated by that current. Generally, lower amplitudes activate smaller nerve fibres that are associated with nociception and proprioception; moderate amplitudes affect intermediate-sized nerve fibres that are responsible for fine motor movements; and higher amplitudes activate the large nerve fibres that produce power in voluntary muscles.<sup>56</sup> The duration that the pulse is present, or pulse duration, is another parameter related to intensity. Summation of amplitude and duration, or the amount of electrical current and its strength, determines the total intensity of the stimulation.<sup>55</sup>

**Frequency:** Refers to the number of pulses delivered in one second and is correlated with the strength of muscle contraction. The higher the frequency of the pulse, the stronger the muscle contraction will be, as there is less time for the muscle to return to a relaxed phase between the pulses. If the frequency is high enough, the produced contraction will not be in the form of separate small contractions but one smooth movement. This type of

contraction is called tetanic contraction, and it is the goal of effective FES treatment due to its ability to produce functional movements in the desired muscles. The minimum frequency that can produce a tetanic contraction is 20Hz; higher frequencies can produce stronger contractions but may result in muscle fatigue more quickly due to the lack of relaxation periods for the muscle fibres.<sup>55</sup>

Pulse shape: There are two pulse shapes that can be used in FES therapy; monopolar and bipolar. Monopolar pulses only include one phase of stimulation, meaning the anode and cathode electrodes are not alternating, while bipolar pulses use two phases of the electrical pulse, where the anode and cathode electrodes are alternating with each pulse. Generally, bipolar pulses are considered to be safer. Bipolar pulses can be symmetrical or asymmetrical. Symmetrical pulses have the same amplitude and duration in opposite polarities while asymmetrical pulses have different amplitude and duration in the opposing polarities. Asymmetrical bipolar pulses enable us to target muscle contraction more precisely as one phase of the pulse is large enough to functionally activate the muscle and the other phase is too small to produce a response. In terms of the balance of the pulse shape, a pulse is called balanced when the total electrical charge delivered to the tissue during the cathodal phase is equal to that during the anodal phase. On the contrary, if the number of electrical currents delivered to the tissue during one phase is larger than the other, the pulse shape is considered non-balanced. Generally, balanced pulse shapes are considered to be safer due to the integrity of the stimulated tissue while non-balanced pulses may cause damage in the tissue as a result of the imbalance of the electrical charge.<sup>55</sup>

## Examples of Pulses Used for Functional Electrical Stimulation



**Figure 2.** Different pulse shapes and their characteristics including polarity, symmetry, and balance. (Image source: Marquez-Chin, C., & Popovic, M. R. (2020). Functional electrical stimulation therapy for restoration of motor function after spinal cord injury and stroke: a review. *Biomedical engineering online*, 19(1), 34. Page 7)

### 1.4.1 FES Cycling

FES cycling includes the use of electrical current on muscles associated with cycling; these muscles can include the gluteal muscles, quadriceps, hamstrings, tibialis anteriors, and gastrocnemii. In FES cycling, a pair of surface electrodes are attached to the above-mentioned muscles and electrical currents are delivered to the targeted muscle, timing the contraction of each to imitate the natural pattern of cycling.

FES cycling enables people with paralyzed or weakened muscles to actively pedal on a stationary bike. There are multiple benefits to FES cycling. By reactivating paralyzed and weak muscles, FES cycling can prevent or even reverse muscle atrophy.<sup>57,58</sup> This effect is



done by forcing the muscles to produce a functional movement against constant resistance.<sup>57,58</sup> FES cycling can enhance muscle strength by increasing neuromuscular conditioning; this means adapting muscles to produce functional movements with greater strength.<sup>58-60</sup> Building endurance in leg muscles is another benefit of FES cycling. This effect is characterized by increasing the duration of the exercise. Endurance is increased through improvements in cardiovascular conditioning (i.e. cardiac output, heart rate, ventilation rate, and VO<sub>2</sub> max).<sup>61,62</sup> VO<sub>2</sub> max or maximal oxygen consumption refers to the maximum amount of oxygen that a person can use during an intense exercise and is indicative of cardiovascular fitness.<sup>63</sup> Additionally, it has been shown that FES cycling can prevent bone loss. This effect is done by delivering force to the bones; as the bike delivers resistance to the muscles it enables them to transfer the load to the bones and create more bone cells.<sup>64-66</sup> Figure 3 represents the main features of the FES bike used in this study.

## Features

- A. Easy-to-use touch screen and software
- B. Stimulators
- C. Adjustable pedals, calf support, crank radius
- D. Adjustable height and tilt platform
- E. Q-Straints safely secure to the RT300



**Figure 3.** Various parts of an FES bike. (Image source: Restorative Therapies. URL: <https://restorative-therapies.com/ifes-systems/rt300-leg-core/>)

### 1.4.2 FES Cycling Effects in SCI

FES cycling has been established as a rehabilitation intervention to improve lower extremity function following SCI. FES cycling can increase the muscle mass and cross-sectional area of leg muscles including quadriceps, adductors, and hamstrings, increasing the voluntary muscle strength and power output.<sup>67,68</sup> Additionally, FES can recruit more muscle fibres compared to voluntary movement alone, and consequently increase the

strength of the muscles.<sup>67,68</sup> Another role that FES cycling plays in increasing the strength is by converting type II fibers to type I fibers, improving resistance to fatigue and reversing muscle atrophy.<sup>69,70</sup> It has been shown that the process of bone mineral loss can be partially reversed using the FES current; after 12 months of cycling, the trabecular and total bone mineral density significantly increased which could result in a lowered risk of fractures.<sup>71</sup> FES cycling has been shown effective in increasing the scores in the International Standards for Neurological Classification of SCI (ISNCSCI).<sup>69,72</sup> In one study, the ISNCSCI motor score was improved by an average of 8.1 points in the active cycling group in comparison to a control group,<sup>69</sup> which is clinically meaningful. In another study, this score was improved slightly (1.7 points) immediately after 3 months of cycling and significantly (4.7 points) at the 3-month follow-up.<sup>72</sup> FES cycling can facilitate neuroplasticity and the motor learning process through the high number of repetitions and sensory feedback provided. Therefore, it can improve functional outcomes, such as gait velocity, spasticity, and Functional Independence Measure (FIM) scores.<sup>72</sup> Overall, evidence suggests that FES cycling is an effective rehabilitation technique to improve neuroplasticity and as a result lower extremity function following an iSCI.

## 1.5 Synergistic Effect of rTMS and FES in Neurological Disorders

Combining rTMS with FES currents is a novel method of treatment that has the potential to enhance plasticity following an iSCI. rTMS is used to increase corticospinal excitability and produce electrical activity in the upper motor neurons (UMN); magnetic fields produced by the TMS machine activate the neurons and trigger them to send an electrical impulse. FES currents are used to activate the lower motor neurons (LMN) by delivering electrical currents to the peripheral nerves at the level of the muscles. It is hoped that stimulation of the UMN followed by stimulation of the LMN will cause facilitation in the synaptic pathways and enhance the electrical pulse conduction; in other words, by using these two interventions sequentially, LTP can be enhanced as a result of firing the neurons repeatedly. Additionally, by applying rTMS prior to FES cycling, it is expected the excitability of the nervous system will be increased and the neural pathways

can be primed, making them more receptive to the FES current. Therefore, this method can facilitate and enhance the process of neuroplasticity. Shariat et al discuss in their communication article how the combination of FES and rTMS can be beneficial for people with stroke; they state that rTMS activates and improves the cortical regions of the nervous system by enhancing the connections between the cells and FES targets the peripheral parts of the nervous system.<sup>73</sup> Using both interventions together appears to result in better functional improvements compared to each of them alone.<sup>73</sup> One study combined the use of FES and rTMS to improve hand function in individuals post-stroke. Participants in this trial were divided into three groups, the rTMS group which received rTMS only, the FES group which received FES only, and the observation group which received both interventions paired sequentially (rTMS prior to FES). The results of this investigation showed that people who received both FES and rTMS experienced greater improvements in their functional tests compared to people in the FES-only and rTMS-only groups. Individuals in the combined intervention group had better scores in their muscle strength and their MEP amplitudes were significantly higher compared to the other two groups, showing improvements in cortical excitability.<sup>74</sup> The combination of rTMS and FES has previously been investigated in individuals with SCI by Fawaz and colleagues to improve hand function.<sup>75</sup> Based on their findings, these two interventions paired with each other led to further improvements in upper limb functional tests compared to FES alone (sham rTMS group). Moreover, the results of this trial showed a significant increase in the amplitude of the MEP and surface electromyography (EMG) recorded from the long flexor muscles of the hand.<sup>75</sup>

## 1.6 Rationale for the Current Study

Although studies have investigated the effects of rTMS and FES cycling on lower limb function independently following iSCI, to our knowledge no studies have looked at the combined effect of these two interventions on lower extremity function in this population. Evidence from similar studies shows promising results which support the combined effect of rTMS and FES, however, the abovementioned trials were done to improve upper extremity function or targeted other populations such as people who have experienced a stroke. Consequently, there is a gap in the literature for studying the

potential effects of combined rTMS and FES cycling and its effects on lower limb function following an iSCI. This case series is part of a pilot trial which serves as a starting point to research the feasibility, safety, and acceptance of pairing rTMS with FES cycling. Additionally, this trial will explore improvements to lower extremity function using outcomes such as walking speed, muscle strength, balance, and other functional tests, comparing the results between the intervention group which will receive active rTMS and FES cycling to the control group which will receive sham rTMS and FES cycling.

## 1.7 Hypothesis

The research questions of this thesis are:

1. What is the feasibility, acceptability, and safety of combining rTMS with FES cycling for lower extremity function following iSCI?
2. Will combining rTMS with FES cycling produce trends towards improved lower extremity function such as gait velocity, muscle strength, and functional measures, compared to FES cycling alone (sham rTMS)?

The current thesis hypothesizes that:

1. The protocol of combining rTMS with FES cycling and using it to improve lower limb function after iSCI is feasible, acceptable, and safe by the participants as measured by: 1) the time taken to complete the recruitment process; 2) the proportion of participants recruited from the total number screened; 3) participant adherence; 4) number of dropouts in each group; 5) willingness of participants to undergo therapy; 6) incidence of treatment-emergent adverse events.
2. Combining active rTMS with FES cycling will produce trends towards greater improvements in gait velocity, muscle strength, and other functional tests compared to FES cycling alone (sham rTMS).

## Chapter 2: Methods

### 2.1 Study Design

This study is a case series description of the first participants in a pilot randomized controlled trial (RCT) (ClinicalTrials.gov ID: NCT05975606). A double-blind design was used in this trial with the participants and the assessors blinded. There were two groups in this study, including the intervention group which received active rTMS followed by FES cycling and the control group which received sham rTMS followed by FES cycling.

### 2.2 Ethical Considerations

This trial was approved by the Western University Research Ethics Board and the Lawson Health Research Institute (Ethics approval letter attached as Appendix A and B). All the participants were provided with a letter of information containing all the required information about the study including the potential benefits and risks of the protocol (Appendix C). Participants were given as much time as they needed to review the information in this letter and were provided with the contact information of the principal investigator (PI) and other researchers of the study for an opportunity to raise any questions or concerns.

### 2.3 Recruitment Process

Participants of this study were recruited from Parkwood Hospital, London, Ontario, Canada. The PI contacted healthcare professionals such as physicians, physiotherapists, and occupational therapists at Parkwood Hospital and asked them to refer their patients who met the inclusion criteria. All three participants of this study were referred to us via a person in their circle of care. Additionally, researchers of this study attended various round meetings at Parkwood Hospital with healthcare professionals working in outpatient SCI and advertised the study. Advertisement posters were printed and installed at different locations in Parkwood Hospital. Lastly, the PI contacted local community organizations, such as Spinal Cord Injury Ontario, to advertise.

## 2.4 Inclusion Criteria

Individuals were eligible for study inclusion if they were (1) adults with iSCI, (2) who had an AIS level of C or D, (3) with a lesion of the injury at any level, (4) resulting from either traumatic or non-traumatic mechanisms, (5) who were in the chronic stage (defined as at least one year post injury; if the injury was of the non-traumatic cause being one year post diagnosis, or in case of a surgery, one year after the surgery), (6) who had non-progressive SCI, and (7) had the self-reported ability to walk independently for 10 meters without the help of another person; the use of gait aids such as cane, walker, and braces was permitted. Participants were asked to fill out a screening questionnaire before being recruited in the study to provide information about their age, sex, gender, level of injury, mechanism of injury, and their AIS score. The screening form is attached as Appendix D.

## 2.5 Exclusion Criteria

Individuals were excluded from the study if they (1) had other neurological or orthopedic complications that affected the lower extremity function, (2) had contraindications for FES (Appendix D), (3) had contraindications for TMS (Appendix D), and (4) had received rTMS before (for the sake of blinding purposes).

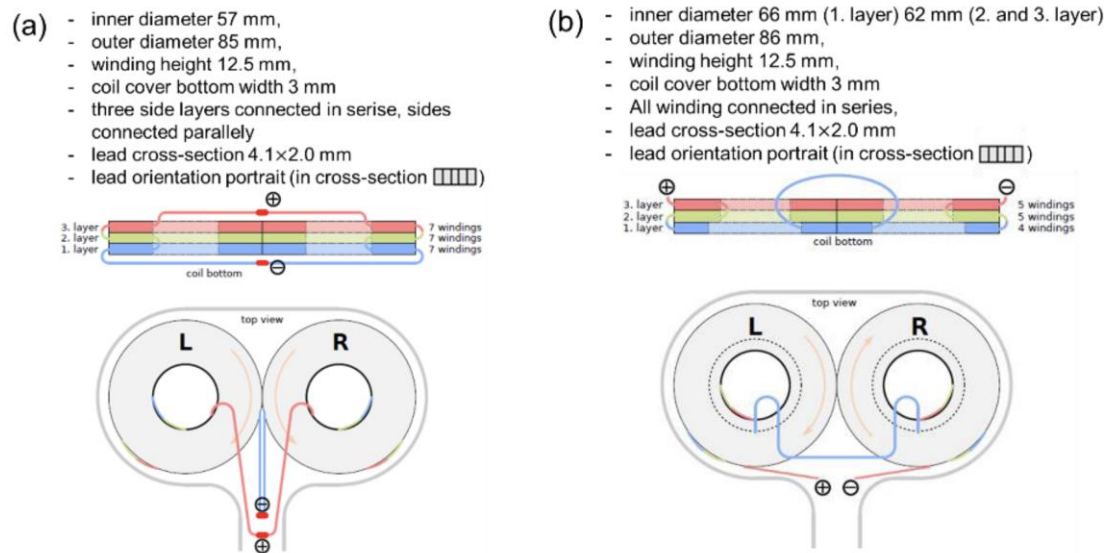
## 2.6 Randomization Process

Participants in this study were randomized to either the intervention or control group using opaque envelopes. Randomization was blocked by four and participants were stratified by their AIS score. A person who was not involved in the study was asked to draw a paper randomly from the envelope at the time of recruitment of the participant.

## 2.7 Blinding Methodology

The rTMS machine used has both an active and a sham coil. The sham coil was used to blind participants in the control group. The sham coil looks the same in colour, shape, and weight as the active coil and produces the same noises. The sham coil causes the same sensations in the body, but the magnetic pulse is not strong enough to evoke a motor response. This is accomplished by off-setting the meeting point of the two magnets in the figure-of-eight coil; in other words, in the sham coil, the magnetic fields are

asynchronized and they never meet in the middle of the coil, therefore, the energy is not concentrated in one area to be strong enough to evoke a response. Figure 4 depicts the inner structures of both active and sham coils.



**Figure 4.** Structure of active and sham coil and their parameters. a) active coil. b) sham coil. (Image source: Takano, M., Havlicek, J., Phillips, D., Nakajima, S., Mimura, M., & Noda, Y. (2021). Development of an advanced sham coil for transcranial magnetic stimulation and examination of its specifications. *Journal of Personalized Medicine*, 11(11), 1058.)

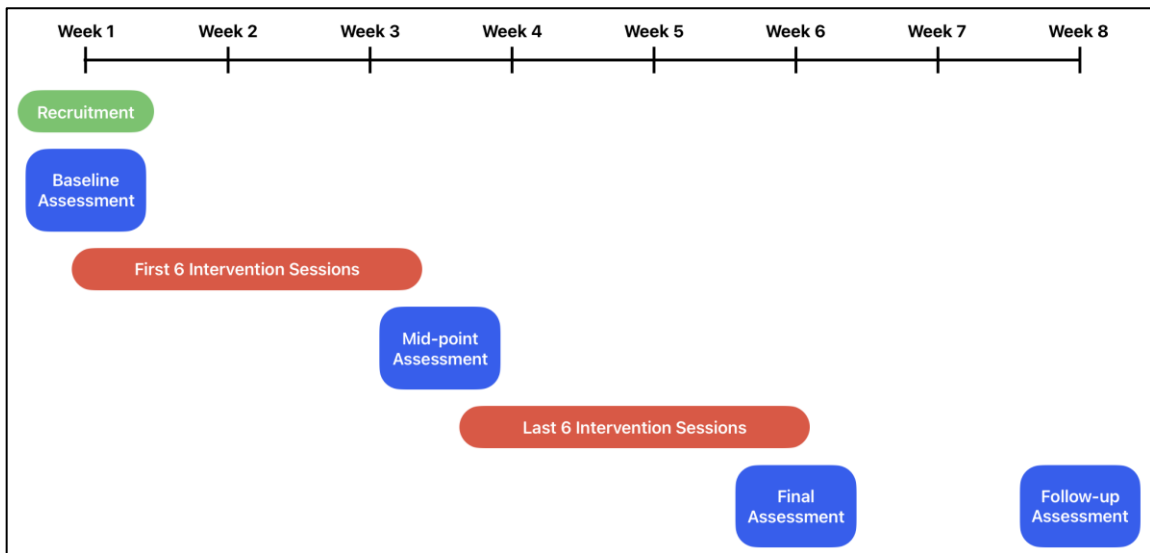
This trial was a double-blind study where the participants and the assessors were blinded. The only person who was aware of the participants' assigned group was the researcher applying the rTMS. At the beginning of each session, the researcher used the active coil to find the participant's hotspot and RMT (these processes are explained in detail in section 2.9). Then the participant was asked to leave the TMS room for a short break; during this time, the researcher changed the active coil to the sham coil if the participant was assigned to the sham group. Therefore, the participant stayed blinded throughout the whole trial. To change the coil from active to sham, the active coil needs to be physically detached and the sham coil should be installed instead. Both coils were kept in the same box, and they were covered throughout the session so the participant could not see them.

To evaluate the efficacy of the blinding process, a blinding questionnaire was designed and used in the follow-up assessment session asking the participants their opinion about

their assigned group and their level of confidence in their choice (explained in detail in section 2.10).

## 2.8 Study Procedures

The study included a total of 12 intervention sessions over a period of six weeks (two sessions per week). Each session lasted approximately 100 minutes with the first 40 minutes assigned to apply the rTMS and the remaining 60 minutes for cycling on the FES bikes. The exception was the first intervention session which took approximately 15 extra minutes that was allocated to finding the hotspot for the first time as well as determining the intensity of the FES electrodes. There were four assessments including one at baseline (before the first intervention session), mid-point (third week, after the sixth intervention session), final (sixth week after the 12<sup>th</sup> intervention session), and follow-up (two weeks after the last intervention session). Each assessment session lasted approximately 60 minutes, and the order of the performed tests was kept the same in every assessment session for integrity of the data. Figure 5 shows the flow of the protocol.



**Figure 5.** Flow of the protocol

## 2.9 rTMS Protocol

rTMS was applied to the M1 area of the brain using the device (DuoMag XT TMS – Cardiff, UK). The first dorsal interosseus (FDI) muscle on the right hand was used for



finding the hotspot and defining the RMT.<sup>47,48,76,77</sup> This muscle was chosen as hand muscles contain numerous sensory fibres and are highly sensitive to stimulation; moreover, they have a large representation in the motor homunculus in the M1 section of the brain making them easier to locate. The high sensitivity of this muscle enables us to use the safest amount of stimulation; when this muscle is used for determining the RMT, we are able to calibrate the intensity of the machine with a highly sensitive muscle, therefore, we can be sure that the stimulation used is safe for other muscles such as the facial muscles that are in close proximity to the coil.

### 2.9.1 Calibration of the Coil

At the beginning of each session, the coil is calibrated to ensure the accuracy and effectiveness of the TMS pulses (i.e. the TMS pulses successfully produce an MEP in the desired muscle). Calibration also helps to ensure that the coil tracker is accurately detected by the neuronavigation camera, confirming the coil is precisely placed on the intended area of the skull. The neuronavigation system combines a camera that detects the globe trackers with a software to map the brain's anatomy to a standard MRI image. This map helps guide the TMS coil to the desired location with accuracy, ensuring that the magnetic pulses are delivered to the intended brain regions. In order to calibrate the coil, it is placed on the floor on a calibration adaptor and the researcher makes sure that the camera is able to detect the coil trackers; then, the calibration process is done through the software.

### 2.9.2 Participant Setup

During the delivery of the rTMS pulses the participant was asked to sit quietly in a chair. Surface electromyography (EMG) was used to record the MEPs produced from the FDI muscle using two electrodes, one active and one reference electrode that are placed on the bulk of the muscle and the tendon of the muscle respectively. A ground electrode was attached to a band wrapped around the participant's wrist which is required for accurately recording the electrical response. Figure 6 indicates the electrode placement location. After placing the electrodes on the FDI muscle, a headband containing three globe

trackers is wrapped around the participant's head. These trackers enable the camera of the neuronavigation device to detect the participant's head.



**Figure 6.** EMG electrode placements for FDI muscle. The black electrode represents the active electrode, the red electrode is the reference, and the green electrode is the ground electrode.

### 2.9.3 Hotspot Location

The first step of delivering TMS was defining the hotspot. The hotspot is the location in the M1 area of the brain that is most correlated with the FDI muscle, represented by the largest MEPs. A common spot on the grid point was selected to begin and the stimulation was demonstrated to the participant using a low intensity of the stimulation (30%) for a single pulse. If the participant was comfortable, the stimulation intensity was increased in increments of 10% until reaching the intensity of 60%. Next, to find the specific hotspot, the stimulation intensity was kept at a moderate level (60%) and three stimulations were delivered to the desired spot. The MEPs from the spot were recorded and averaged to define the final MEP for that location. This process was done for multiple adjacent spots and the MEPs compared. The location with the highest magnitude MEPs was considered the hotspot and this location was used to deliver the rTMS stimulation for the session. The process of finding the hotspot was done at the beginning of every session, typically the hotspot remained consistent for each participant in the subsequent sessions.

#### 2.9.4 Finding the RMT

The next step was to measure the resting motor threshold or RMT; RMT is the minimum intensity that is needed to evoke a response in a muscle as a result of a single pulse of TMS.<sup>78</sup> This value is useful in setting the amount of intensity that should be used for delivering rTMS pulses safely; a fraction of this amount of stimulation is used to ensure that the intensity of the stimulation will not lead to muscle twitches or seizures. For determining the RMT, single pulses of TMS are delivered to the hotspot and the lowest intensity that elicited a response of at least 50 $\mu$ V in at least five consecutive trials out of ten, is considered as the RMT level.<sup>79</sup>

#### 2.9.5 rTMS Delivery

Once the hotspot and RMT were determined the participant was ready for the rTMS delivery. Before starting this stage, the participant was asked to leave the TMS lab, allowing the researcher to change the active coil to the sham coil if the participant was in the control group. The parameters of the stimulation used in this trial are described in Table 2.

**Table 2.** TMS parameters

Stimulation type	Burst
Number of pulses in each burst	3
Pulse frequency	20 Hz
Number of bursts in each train	40
Burst frequency	1 Hz
Number of trains	15
Inter-train interval	28 seconds
Stimulation intensity	90% of RMT level
Total time of the intervention	17 minutes

The researcher first described what to expect with rTMS to the participant, followed by an example of the stimulation done away from them and then one example train on the skull; if they found this protocol comfortable, the stimulation started. The researcher regularly checked in with participants to ensure they were feeling comfortable. Earplugs were provided to the participants if they found the noise of the device disturbing. After

the experiment, the electrodes were removed from the skin and rubbing alcohol was provided to remove residue from the skin followed by skin lotion if desired.

## 2.10 FES Protocol

FES bikes (Restorative Therapies RT300 – New Hampshire, USA) were used to deliver FES currents to five muscle groups on each side including the gluteus maximii, quadriceps, hamstring, tibialis anterior, and gastrocnemii using surface electrodes attached to the muscle bellies. During the first session, the researcher determined the amplitude of the intensity that was comfortable for the participant by gradually increasing the stimulation intensity until a visible contraction of the target muscle was seen, and the participant reported the sensation to be tolerable. The setting and stimulation intensities were saved for each participant and the same settings were used in subsequent sessions unless the participant requested adjustments for the intensity of each of the electrodes to either a higher or lower amplitude.

The FES was scheduled for 60 minutes, with 15 minutes for setting up and approximately 40-45 minutes of cycling time. The target speed of cycling was 30-35 revolutions per minute (RPM) and the resistance of the bike ranged from 5-15 N; the bike is responsive to the amount of force that the participant is applying. In other words, the bike will automatically provide more resistance if the participant is pushing harder to keep the speed constant. On the contrary, if the participant is using less force, the bike will use less resistance and more force from the pedals to help keep up the speed; this way the bike ensures that the cycling speed is kept constant. The therapy aims to increase the active time and reduce the passive time. Active time is the amount of time that the participant is actively cycling and using their muscle force and passive time is the amount of time that the force generated by the participant's muscles is not enough and the bike is passively helping the participant to cycle. At the end of the trial information about the cycling parameters was collected; these parameters include total cycling distance, expended energy, average power, and active and passive time.

## 2.11 Primary Outcome Measures

The outcome measures were divided into two groups, primary and secondary. Primary outcomes included feasibility, acceptability, and safety of combining rTMS with FES cycling to improve lower extremity function following iSCI. To measure the feasibility of this protocol, (1) the time taken to complete the recruitment of three participants and (2) the proportion of participants recruited from the total number screened, were collected. To measure the acceptability of this protocol (1) the total number of sessions attended by each participant, (2) the number of dropouts in each of the intervention and control groups, and (3) the willingness of participants to undergo therapy, were collected (willingness to participate questionnaire is attached as Appendix E). This questionnaire rated participants' willingness to participate in the study at the beginning of the study on a Likert scale from 0 as not willing at all to 10 as absolutely willing. To measure the safety of this protocol, (1) the incidence of treatment-emergent adverse events and (2) their duration were collected.

## 2.12 Secondary Outcome Measures

Secondary outcome measures included lower extremity functional tests, which were collected by a blinded assessor who was a registered physical therapist. These outcome measures are divided into three groups including instrumented outcomes, clinical outcomes, and questionnaires.

### 2.12.1 Instrumented Outcome Measures

Instrumented outcome measures consist of lower extremity functional tests that were performed using specific equipment. A pressure sensor gait mat (ProtoKinetics – Pennsylvania, USA) was used to perform the walking test. The participant was asked to walk two passes on a 7-meter-long gait mat at a pace that they were comfortable with. Participants were allowed to use any gait aids to perform the test such as a cane, walker, or braces but they were asked to do the test independently without the help of another person. The data collected from the gait mat include walking speed, step length, step width, and cadence (number of steps per minute). The minimal clinically important difference (MCID) value for gait velocity is identified as 0.05m/s in the SCI population.<sup>80</sup>

MCID value for step length is 17cm according to Mohandas;<sup>81</sup> and this value is not measured for step width in SCI population. MCID for cadence is identified as 13 steps/minute in this population.<sup>81</sup> Inertial measurement units (IMUs) (APDM Wearable Technologies – Oregon, USA) were used to perform four functional tests. Six sensors were placed on the body (wrists, feet, lower back, and sternum). Functional tests performed included the Timed-Up-and-Go (TUG), 5-times Sit-to-Stand (STS), and quiet standing with feet apart on a firm surface both with eyes open and with eyes closed. The TUG test asks participants to stand up from a seated position on a chair without using their arms, walk forward 3 meters, turn 180 degrees, walk back to the chair, turn 180 degrees, and sit down on the chair; the total duration of this trial is measured in seconds. This test was shown to be valid and reliable in the SCI population.<sup>82,83</sup> 5-times STS test includes asking the participant to stand up from a seated position on a chair without using their arms, sit back down with their back against the back of the chair, and repeat this action five times; the total duration of this trial is measured in seconds. The MCID value of this test is measured as 2 seconds for the SCI population.<sup>84</sup> Quiet standing with feet apart on a firm surface has the participant stand comfortably with their feet in a standardized position with their hands on their hips for 30 seconds; the mean sway velocity is measured in meters per second (m/s) in this test.

### 2.12.2 Clinical Outcome Measures

Clinical outcome measures include the tests that were performed by a blinded physical therapist. Lower Extremity Muscle Score (LEMS) evaluates the strength of five muscle groups based on a six-point scale. Table 3 depicts the key muscle groups and the related spinal roots that are tested, and Table 4 describes the grading of the LEMS scale. The final score of this test is calculated by summing the score of each muscle group on each side (five muscle groups on each side with a maximum score of 5 for each muscle). The total score, therefore, is calculated out of 50.<sup>85</sup> The MCID value of this test is 3.66 in the SCI population.<sup>86</sup> Walking Index for Spinal Cord Injury (WISCI) II grades a person with SCI's walking ability based on the physical assistance or the gait aid used out of a total score of 20. This test is shown to be valid and reliable in the SCI population.<sup>87</sup> Table 5 describes the grading criteria.<sup>88</sup>

**Table 3.** Muscle groups tested in LEMS and their related spinal roots

Spinal root	Muscle group
L2	Hip flexors (iliopsoas and rectus femoris)
L3	Knee extensors (quadriceps)
L4	Ankle dorsiflexors (tibialis anterior)
L5	Long toe extensors (extensor hallucis longus)
S1	Ankle plantar flexors (gastrocnemius and soleus)

**Table 4.** LEMS grading criteria

Grade	Description
0	Total paralysis
1	Palpable or visible contraction
2	Active movement, full range of motion (ROM) when gravity is eliminated.
3	Active movement, full ROM against gravity.
4	Active movement, full ROM against gravity, and moderate resistance in muscle-specific position.
5	(Normal) Active movement, full ROM against gravity, and full resistance in a muscle-specific position expected from a healthy person.
5*	(Normal) Active movement, full ROM against gravity, and sufficient resistance to be considered normal if identified inhibiting factors (i.e., pain, disuse) were not present.
NT	Not testable (i.e., due to immobilization, severe pain that can prevent the grading of the patient, amputation of the limb, or contracture of >50% of the range of motion).

**Table 5.** WISCI-II grading criteria

Grade	Description
0	Client is unable to stand and/or participate in assistant walking.
1	Ambulate in parallel bars, with braces and physical assistance of two persons, less than 10 meters.
2	Ambulates in parallel bars, with braces and physical assistance of two persons, 10 meters.
3	Ambulates in parallel bars, with braces and physical assistance of one person, 10 meters.
4	Ambulates in parallel bars, no braces and physical assistance of one person, 10 meters.
5	Ambulates in parallel bars, with braces and no physical assistance, 10 meters.
6	Ambulates with walker, with braces and physical assistance of one person, 10 meters.

7	Ambulates with two crutches, braces and physical assistance of one person, 10 meters.
8	Ambulates with walker, no braces and physical assistance of one person, 10 meters.
9	Ambulates with walker, with braces and no physical assistance, 10 meters.
10	Ambulates with one cane/crutch, with braces and physical assistance of one person, 10 meters.
11	Ambulates with two crutches, no braces and physical assistance of one person, 10 meters.
12	Ambulates with two crutches, with braces and no physical assistance, 10 meters.
13	Ambulates with walker, no braces and no physical assistance, 10 meters.
14	Ambulates with one cane/crutch, no braces and physical assistance of one person, 10 meters.
15	Ambulates with one cane/crutch, with braces and no physical assistance, 10 meters.
16	Ambulates with two crutches, no braces and no physical assistance, 10 meters.
17	Ambulates with no devices, no braces and physical assistance of one person, 10 meters.
18	Ambulates with no devices, with braces and no physical assistance, 10 meters.
19	Ambulates with one cane/crutch, no braces and no physical assistance, 10 meters.
20	Ambulates with no devices, no braces and no physical assistance, 10 meters.

### 2.12.3 Questionnaires

Two subjective outcome measures were evaluated through questionnaires. The Global Rating of Change (GRC) scale asked the participant to rate the improvement of their walking abilities and overall recovery of their lower limb function from the time that they began the intervention until the current time on a scale from -7 to +7. This questionnaire was completed in the last three assessment sessions. Table 6 depicts the items of this questionnaire. The blinding questionnaire asked the participant to indicate which study group they believed they were assigned to (active or sham) and rate their confidence in their group allocation on a scale of 1 to 10, with 1 being “Not at all confident” and 10 being “Very confident”. This questionnaire was completed in the last assessment session.



Finally, they were asked to optionally provide any additional comments or thoughts about their group allocation perception.

**Table 6.** GRC questionnaire items

<b>Grade</b>	<b>Description</b>
+7	A very great deal better
+6	A great deal better
+5	Quite a bit better
+4	Moderately better
+3	Somewhat better
+2	A little bit better
+1	A tiny bit better (almost the same)
0	About the same
-1	A tiny bit worse (almost the same)
-2	A little bit worse
-3	Somewhat worse
-4	Moderately worse
-5	Quite a bit worse
-6	A great deal worse
-7	A very great deal worse

## 2.13 Data Analysis

Gait mat data were collected and analyzed through an (Excel) macro which provided data on gait velocity, step length, step width, and cadence. Functional tests data were collected through IMUs and analyzed through Mobility Lab software (APDM Wearable Technologies - Portland, USA); this software provided information such as the total time of the trial for TUG and STS tests and the sway velocity of the quiet standing tests. Clinical outcomes were collected by a registered physiotherapist and recorded on (Excel) line graphs. Cycling parameters including the average power were collected through the (Restorative Therapies - New Hampshire, USA) software and provided at the end of each session. Descriptive statistics were used in this study to analyze the collected data, as due to its case series design no statistical testing could be completed.

## Chapter 3: Results

### 3.1 Demographic Information

Three participants were recruited for this case series; Table 7 depicts the demographic information of the participants. Notably, rTMS03 had a history of stroke predating his SCI diagnosis. However, he met the inclusion criteria as he self-reported full recovery of lower extremity motor function following the stroke.

**Table 7.** Demographic information of the participants

<b>Participant ID</b>	<b>Age</b>	<b>Sex</b>	<b>Gender</b>	<b>Level of Injury</b>	<b>AIS Level</b>	<b>Mechanism of Injury</b>	<b>Group</b>
rTMS01	22	Male	Man	T6	C	Traumatic	Sham
rTMS02	42	Male	Man	T3-T6	D	Non-traumatic	Active
rTMS03	84	Male	Man	C	D	Non-traumatic	Active

### 3.2 Primary Outcome Measures

#### 3.2.1 Feasibility

The recruitment process started in August 2023 and ended in February 2024. The total timeframe of the recruitment was five months and three weeks for all three participants. The rate of recruitment was about one participant every five weeks. Five individuals were screened in total with three participants consenting to take part in the study (recruitment rate of 60%). Of the two potential participants who did not participate in the study one person declined due to the use of brain stimulation and the other person did not meet the eligibility criteria as they were AIS level B and unable to walk independently for 10 meters.

#### 3.2.2 Acceptability

The overall adherence rate for all participants, including both treatment and assessments, was 93.7%; notably, the second and third participants had a 100% adherence rate while the first participant missed two intervention sessions and one assessment session due to unrelated medical issues. The total number of intervention sessions for the third

participant, rTMS03, was eight due to equipment issues that ended the study protocol. The final two assessment sessions for this participant were held earlier than planned per protocol, after the eighth intervention session. There were no dropouts in any of the groups showing a compliance rate of 100%. The mean willingness to participate score was 9.3 out of 10, indicating continued interest throughout the study.

### 3.2.3 Safety

Table 8 depicts the rate and duration of adverse events for all the participants. Adverse events in this study included minor headaches experienced by two of the participants and redness of skin under the FES electrodes experienced by one participant, all of which are anticipated risks of taking part in these interventions.<sup>89,90</sup> Each incident resolved spontaneously without any medical interventions. One participant did not report any adverse events throughout the protocol.

**Table 8.** Adverse events descriptions

<b>Participant ID</b>	<b>Adverse Event</b>	<b>Duration</b>	<b>Session #</b>	<b>Frequency</b>
rTMS01	Headache on opposite side	Several hours	3	Once
rTMS02	Headache on stimulated side	Several minutes	4	Once
	Skin redness under FES electrodes (without temperature difference)	~24 hours	4	Once

## 3.3 Secondary Outcome Measures

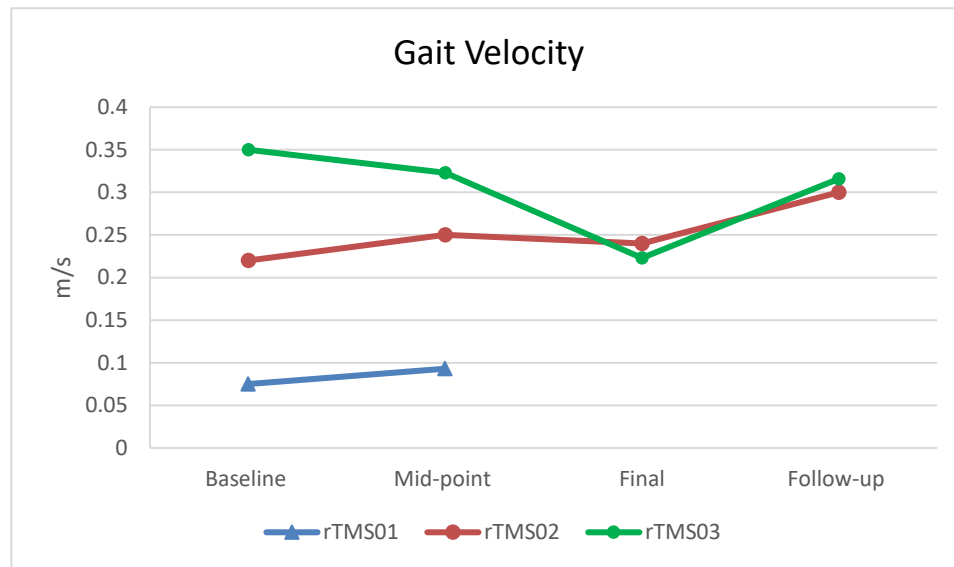
### 3.3.1 Missing Data

One participant, rTMS01, missed the final assessment session and was not able to perform the functional tests on the follow-up assessment session due to the unavailability

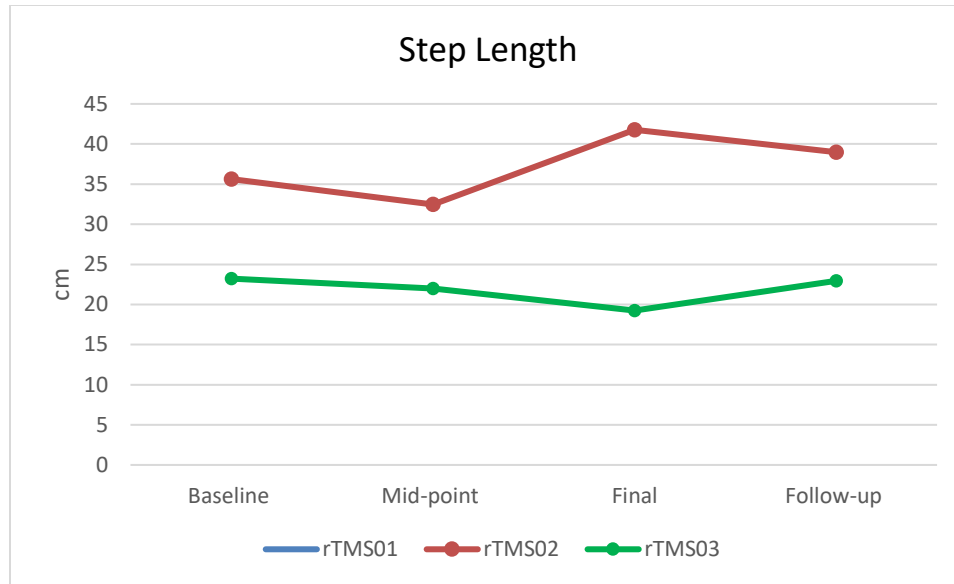
of his gait aid (braces). As a result, all the functional data for this participant was obtained during the baseline and mid-point assessment sessions. This participant also missed the 8<sup>th</sup> and 12<sup>th</sup> intervention sessions, and he did not complete the FES cycling portion of the session on the 9<sup>th</sup> intervention session all due to unrelated medical issues. These missed data points are reflected in Figure 18 regarding cycling power.

### 3.3.2 Gait Parameters

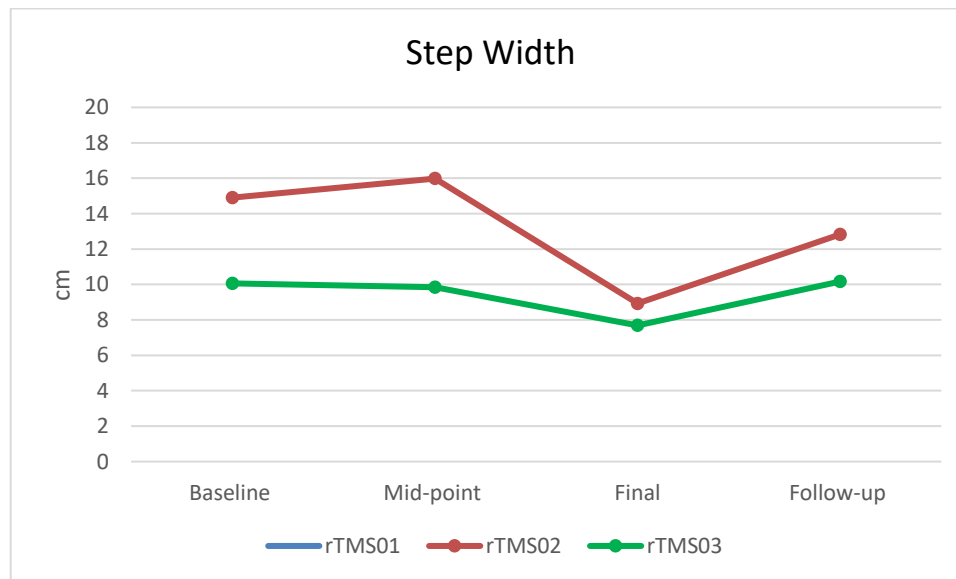
Figures 7 to 10 depict the gait parameters of all participants. It should be noted that for rTMS01 the value of step length and step width for the mid-point assessment session was not recorded due to technical difficulties with the gait mat. The value of step length at the baseline assessment session was 25.956cm, and step width was 18.302cm. Since only one data point exists, drawing a chart for this participant is not feasible. In subsequent figures, the triangle data points represent the sham participant (rTMS01), and the circle shapes represent the active group participants (rTMS02 and rTMS03).



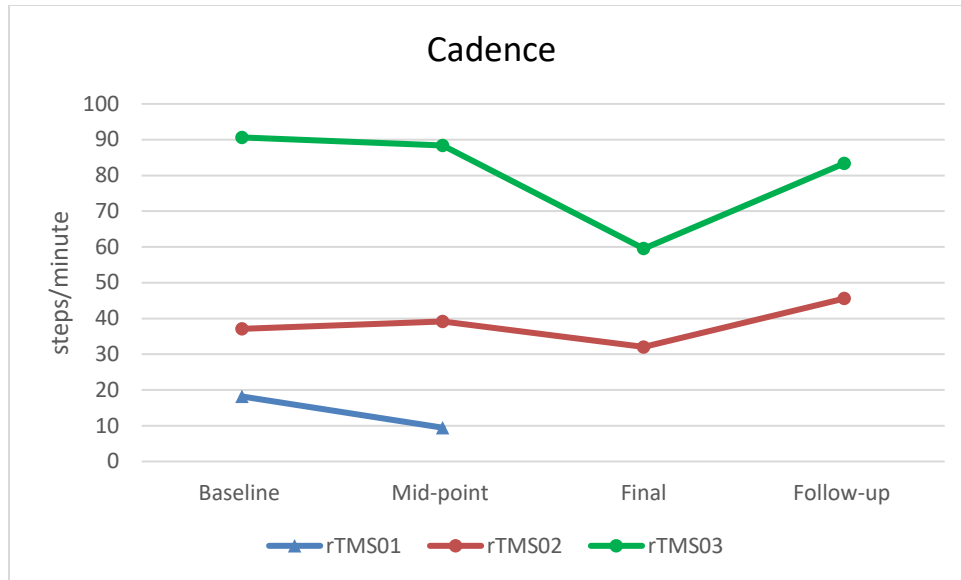
**Figure 7.** Gait velocity for participants in meters per second (m/s). Higher values represent better performance.



**Figure 8.** Step length for participants in centimeters (cm). Higher values represent better performance.



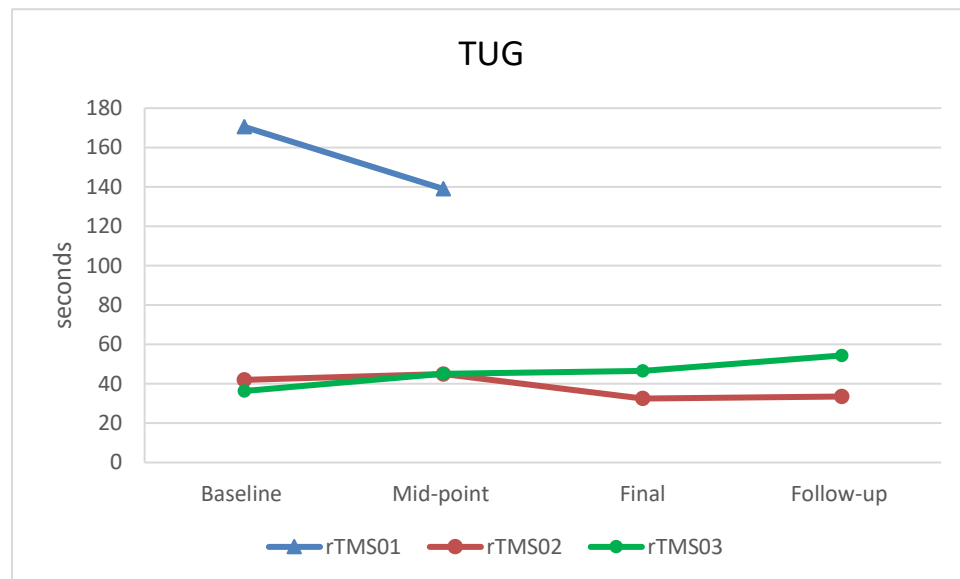
**Figure 9.** Step width for participants in centimeters (cm). Lower values represent better performance.



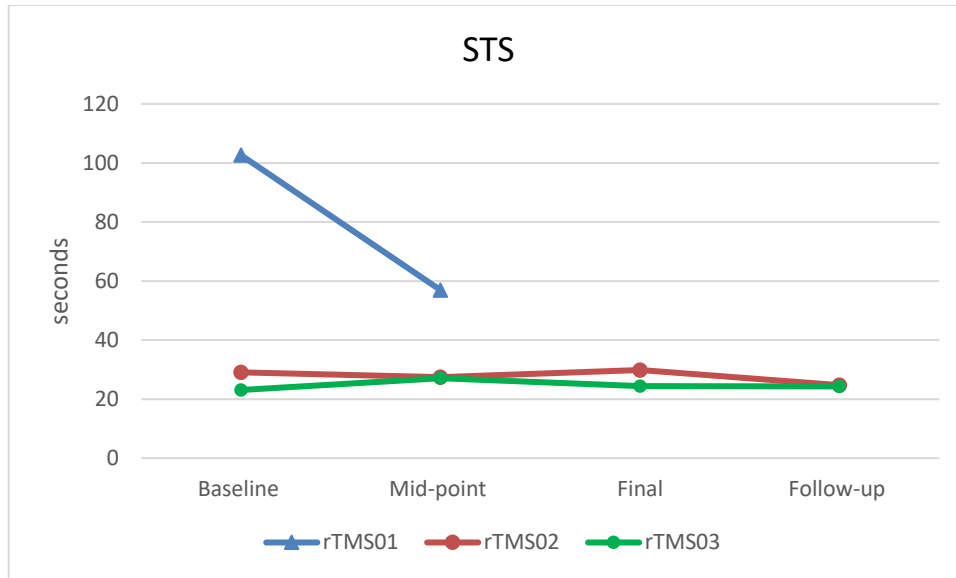
**Figure 10.** Cadence for participants in steps per minute. Higher values represent better performance.

### 3.3.3 Functional Tests

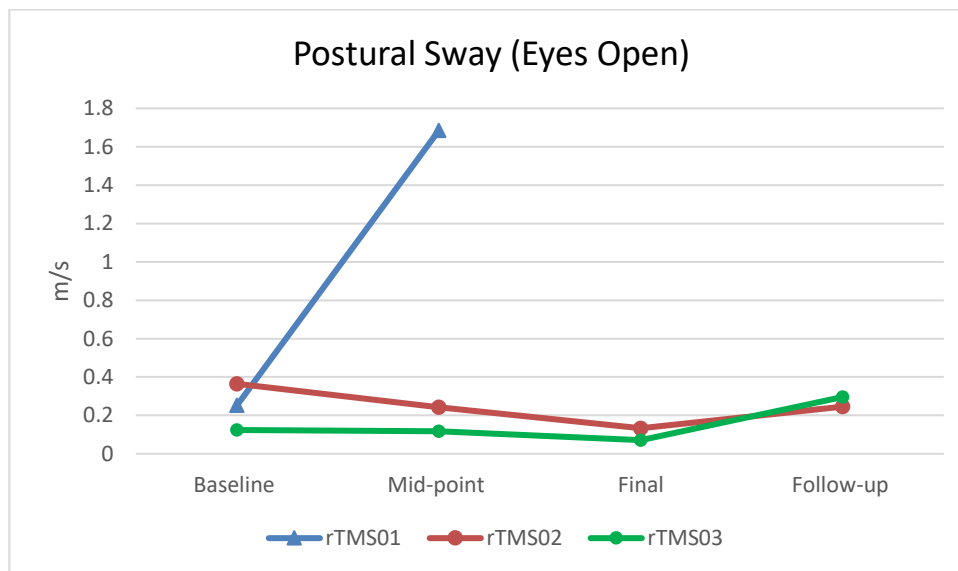
Figures 11 to 14 show the results of functional tests for all participants.



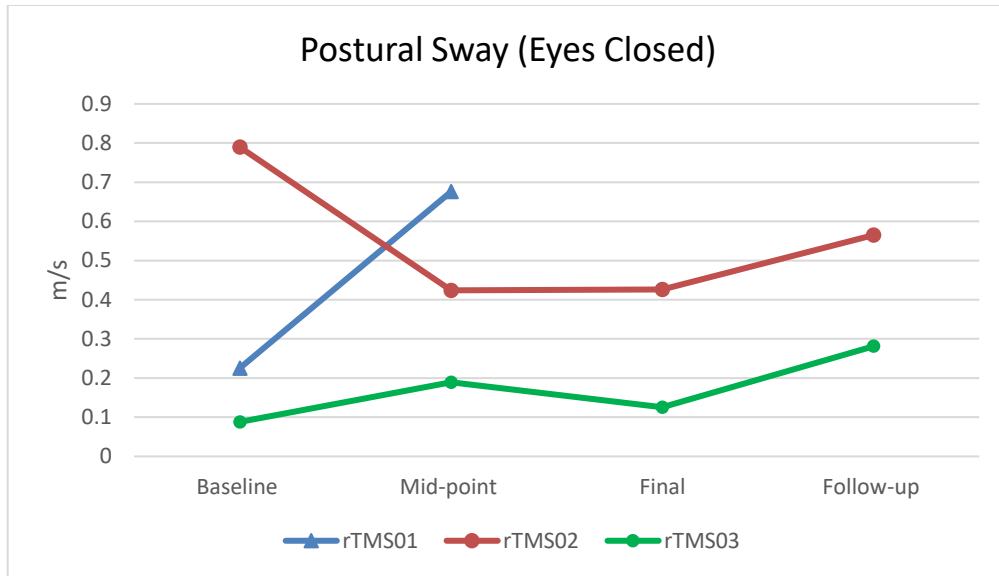
**Figure 11.** Timed-Up-and-Go (TUG) test scores for participants in seconds. Lower values represent better performance.



**Figure 12.** Sit-to-Stand (STS) test scores for participants in seconds. Lower values represent better performance.



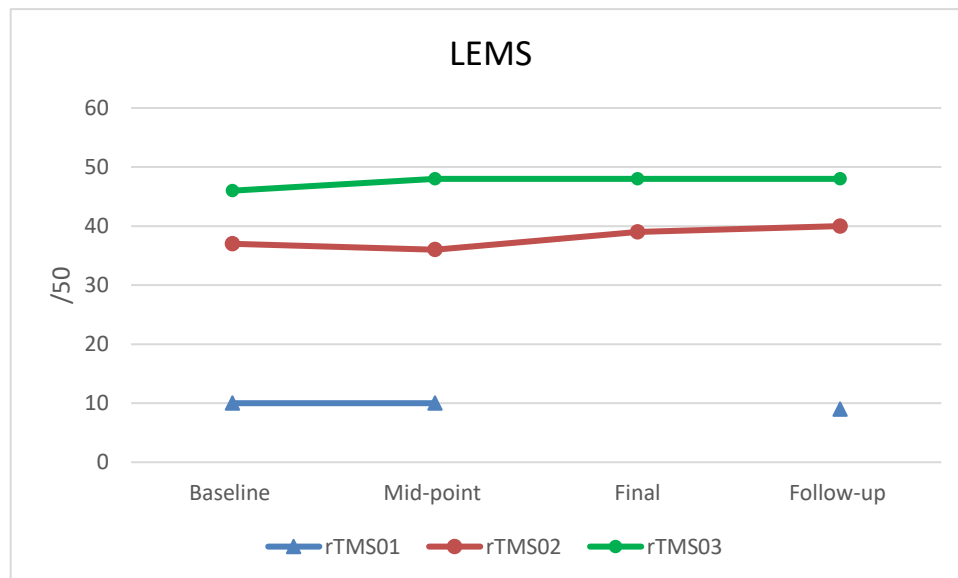
**Figure 13.** Postural sway velocity with eyes open for participants in meters per second (m/s). Lower values represent better performance.



**Figure 14.** Postural sway velocity with eyes closed for participants in meters per second (m/s). Lower values represent better performance.

### 3.3.4 Clinical Tests

Figure 15 shows the results of LEMS for all participants. WISCI-II scores remained the same for all participants throughout the sessions.



**Figure 15.** Lower Extremity Motor Scores (LEMS) for participants out of a total of 50 points. Higher values represent better performance.



### 3.3.5 Questionnaires

Table 9 depicts the GRC scores of each participant and Table 10 shows the results of the blinding questionnaire and participants' real group assignment.

**Table 9.** GRC scores

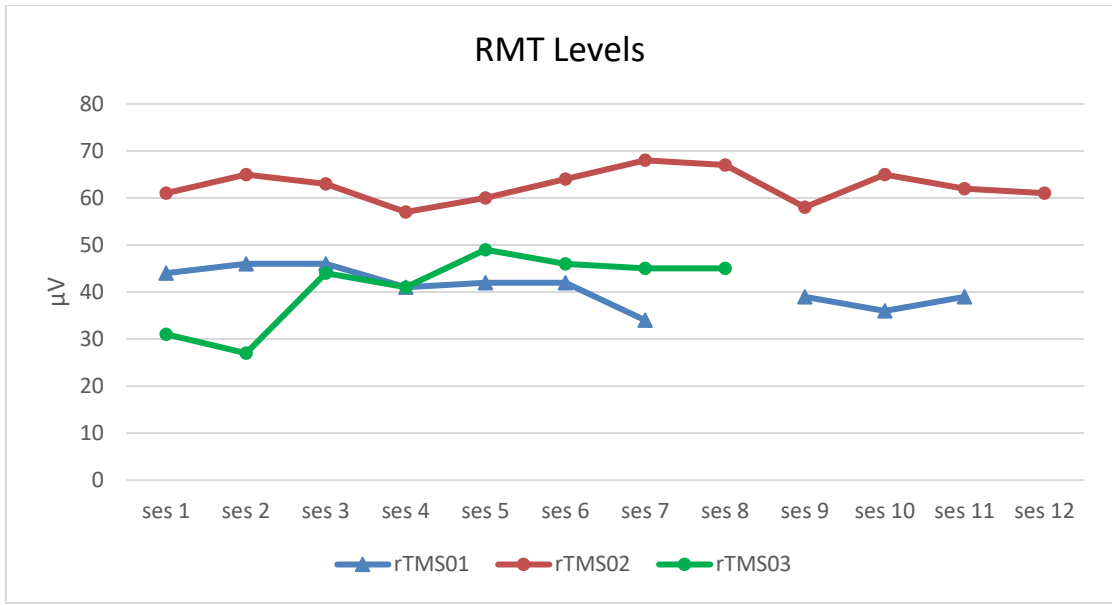
<b>Participant ID</b>	<b>Mid-point</b>	<b>Final</b>	<b>Follow-up</b>
rTMS01	+5	missed	+4
rTMS02	+4	+3	+4
rTMS03	0	0	+3

**Table 10.** Blinding questionnaire results

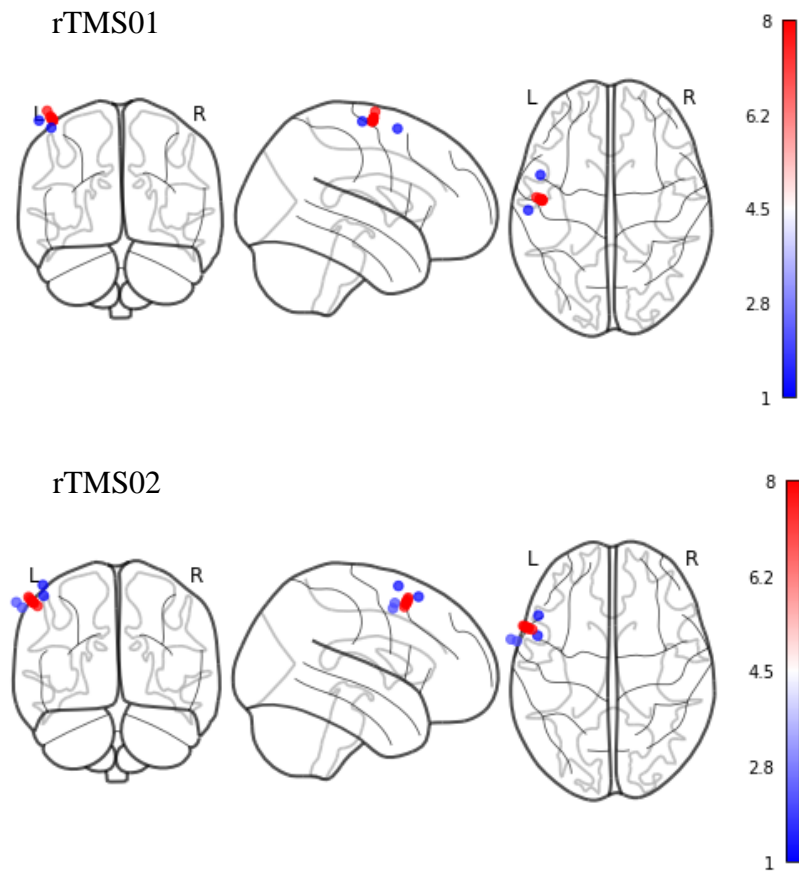
<b>Participant ID</b>	<b>Assigned Group</b>	<b>Perceived Group</b>	<b>Confidence</b>
rTMS01	Sham	Active	10
rTMS02	Active	Active	8
rTMS03	Active	Sham	2.5

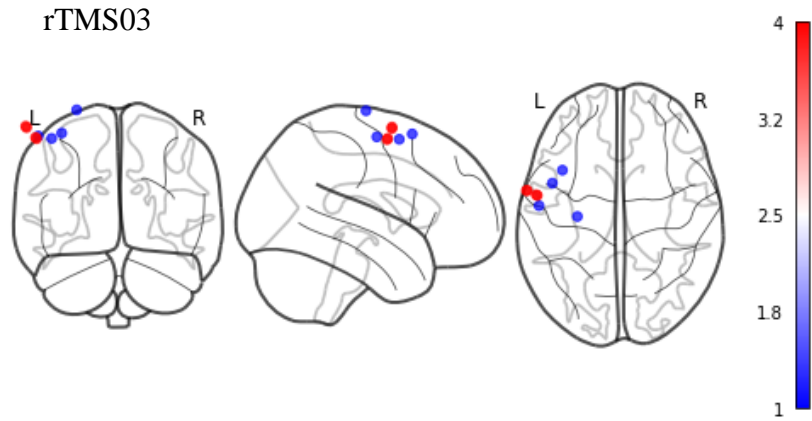
## 3.4 TMS Parameters

Although reporting the data of TMS parameters was not originally planned in the protocol, it has been included due to the importance of this data in further explaining each participant's progress through the protocol. Figure 16 shows the RMT level recorded from all participants during each intervention session. A consideration is that rTMS03 exhibited a heightened sensitivity to rTMS during the process of recording the threshold. This necessitated the research team to use a lower stimulation intensity for this participant during the first two intervention sessions. Figure 17 is a heat map showing the hotspot location for the FDI muscle of all participants across the treatment sessions.



**Figure 16.** RMT levels of participants in  $\mu\text{V}$

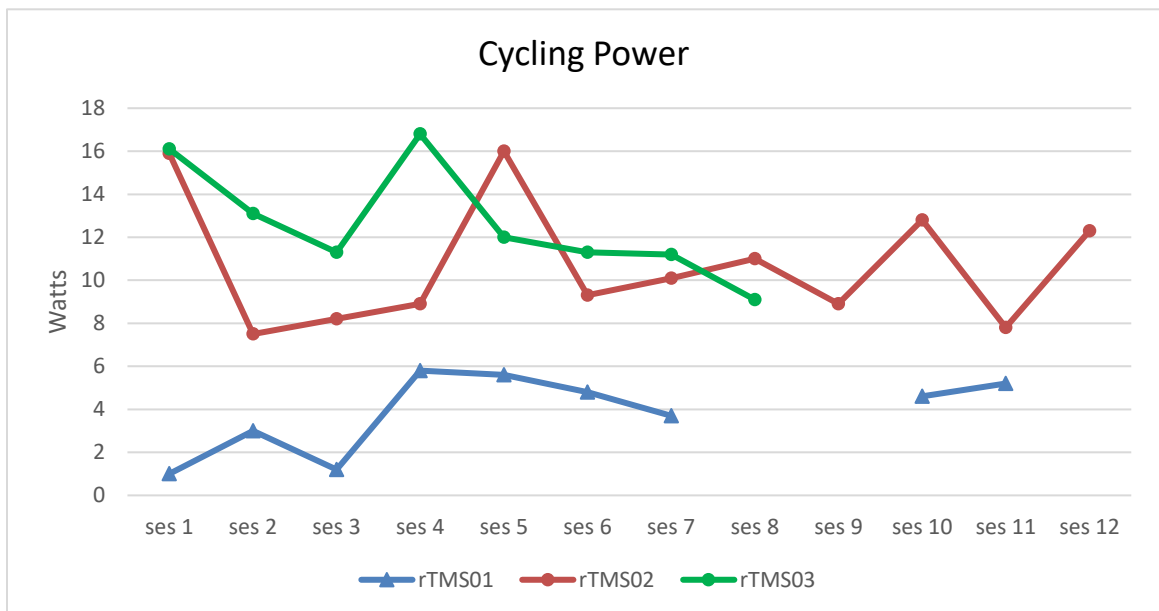




**Figure 17.** Hotspot coordinates for participants. The colour bar and the numbers beside it show the frequency of the hotspots.

### 3.5 Cycling Parameters

Figure 18 shows the cycling power trend for all participants throughout the protocol.



**Figure 18.** Cycling power for participants in Watts. Higher values represent better performance.

## Chapter 4: Discussion

### 4.1 Key Findings

This study was the first experiment to our knowledge, to combine rTMS with FES cycling following iSCI. It was hypothesized that the protocol would be feasible, well-accepted, and safe. Additionally, we hypothesized that lower extremity function would show greater improvements in the intervention group compared to the control group.

#### 4.1.1 Feasibility, Acceptability, and Safety

Results of this trial indicated pairing rTMS with FES cycling in the iSCI population is feasible, however, it is important for future trials to plan appropriate study timelines, as our preliminary findings suggest a recruitment rate of about one participant every five weeks with a 60% recruitment rate. It is worth mentioning that the sample size of this study was small and therefore the percentage of recruitment might not be a true representative of the actual proportions in a larger study. In a similar study done by Krogh et al, the timeframe for recruiting 20 participants was approximately 20 months (one participant every four weeks); and the recruitment percentage was ~71%.<sup>76</sup>

The total adherence rate of the protocol was 93.7%. However, two participants had 100% adherence. Accordingly, these findings also demonstrated high compliance, with zero dropouts from either active or sham groups. According to previous literature, an attendance rate of >80% and a dropout rate of <20% is considered feasible.<sup>91</sup> This indicates that the protocol used in this trial was feasible for the iSCI population. Moreover, the total willingness to participate score was 9.3/10. Scores of 7-10 are considered as highly willing,<sup>92</sup> meaning the results of this trial show a high interest in participating in this protocol by individuals with iSCI.

Data regarding the safety of the protocol showed two minor adverse events including headaches and redness of the skin under the FES electrodes. One of the headache incidents occurred to the participant enrolled in the sham treatment and was on the opposite side of the head stimulated by the coil; therefore, this incident was most likely not related to the stimulation. It is possible the headache was due to maintaining a static

neck position for the duration of the protocol. The reported rate of headache incidents based on a systematic review of the application of rTMS in a stroke population ranged from 33-66%.<sup>89</sup> These headaches were found to be moderate intensity, transient (lasting ~3 hours), and resolved in five sessions.<sup>89</sup> Rate of headaches for participants in the active treatment group was infrequent in our study, with a headache occurring in one participant during one session out of the total 20 sessions of active treatment, which is equal to 5%, and is lower than the reported values in the literature. Other possible adverse events as a result of rTMS include scalp pain and discomfort, muscle twitches, and nausea<sup>93,94</sup> which were all absent in our study. Skin redness under the FES electrodes occurred during one session out of the total 32 sessions across all participants, which equals 3.1%. The literature suggests that this event is infrequent and ranges from 1-3%,<sup>90</sup> which aligns with our findings. Other adverse events associated with FES cycling such as increased spasticity, ischial hematoma, and autonomic dysreflexia<sup>70</sup> were all absent in our protocol. Overall, the findings of our study confirm the first hypothesis that pairing rTMS with FES cycling in individuals with iSCI is feasible, well-accepted, and safe.

#### 4.1.2 Lower Extremity Function

It is difficult to interpret the difference between the intervention and control group in this case series, as the only sham participant in our protocol was not able to complete the final assessment session and was only able to complete the questionnaires and LEMS during the follow-up assessment session. Therefore, the ability of this study to distinguish between the active and sham treatment results is insufficient.

It is noted that the results of lower extremity outcome measures for rTMS01 are reported from baseline to mid-point assessment session; for rTMS02 and rTMS03 outcomes are reported from baseline to final assessment session and the trend to follow-up session is reported subsequently. The results show that gait speed trended towards improvements in rTMS01 from baseline to mid-point, however, this change did not surpass the MCID value (0.05m/s) identified for the SCI population.<sup>80</sup> For rTMS02, the trend showed improvement to final assessment session, but it did not reach the MCID value, however, the improvement sustained and surpassed the MCID in the follow-up assessment session. This parameter showed a negative trend (reaching the MCID) for rTMS03 until the final

assessment session and returned to baseline in the follow-up. Cadence decreased in both the sham participant and rTMS03, with the change surpassing the MCID (13.0 steps/minute) for rTMS03. However, this trend reversed for rTMS03, and an increase was observed in the follow-up session, surpassing the MCID by 23.8 steps/minute from the final assessment to follow-up. This parameter decreased slightly for rTMS02 to the final assessment session without reaching the MCID and improved in the follow-up session to more than the baseline value, however, this improvement did not surpass the MCID. Step length showed an increasing trend for rTMS02 to the final assessment, and it decreased in the follow-up assessment, however, the value in the follow-up session was still higher than baseline. This parameter initially decreased for rTMS03 to the final assessment and returned to baseline in the follow-up session. The MCID value for this parameter is SCI population is 17cm,<sup>81</sup> which was not achieved by any participants. Similarly, step width improved in rTMS02 to the final session, and it showed a negative trend in the follow-up session; and it initially showed a decrease for rTMS03 but returned to baseline later during the follow-up assessment.

Results of the TUG test showed improvement for rTMS01 by 31.53s. For rTMS02 this value improved by 9.51s and the increase was continued by 1.1s to the follow-up session. A negative trend for rTMS03 was observed by -10.2s in the final assessment and the negative trend continued to the follow-up assessment by -7.88s. The MCID value of this parameter has not been determined in the SCI population, making it difficult to understand the meaningfulness of these changes. The STS test was improved in rTMS01 by 45.73s and surpassed the MCID value (2s).<sup>84</sup> rTMS02 remained stable to the final assessment and improved by 4.3s reaching the MCID in the follow-up session. This parameter remained stable in rTMS03 through final assessment and deteriorated by 1.2s in the follow-up session without reaching the MCID. Postural sway velocity with eyes open showed a negative trend for rTMS01, while it showed improvements in rTMS02 without the maintenance effects (0.23m/s improvement until the final assessment and deteriorated by 0.11m/s to the follow-up assessment). rTMS03 improved in this test to the final assessment but deteriorated in the follow-up session. The same test with eyes closed showed a negative trend for rTMS01 by 0.44m/s, and rTMS03 by 0.04m/s in the final assessment and then 0.16m/s to the follow-up session and improved in rTMS02

without the effects sustaining through the follow-up session (improved by 0.36m/s up to final assessment and deteriorated by 0.14m/s at follow-up).

WISCI-II scores remained unchanged for all participants, which could be expected due to the high degree of functional change required to increase scores on this assessment. The LEMS score was decreased by one point for the sham participant in the follow-up assessment and increased for rTMS02 by 2 points to the final session and one point in the follow-up session; however, this improvement did not reach the MCID value (3.66) in this population.<sup>86</sup> This score showed an initial improvement for rTMS03 by 2 points but remained unchanged after the mid-point assessment session, however, this participant started with the highest score (46) and may have experienced ceiling effects.

Some changes were observed in cycling power for participants throughout the protocol, which can be another measure of lower extremity strength and function. Cycling power was improved for rTMS01, remained the same for rTMS02, and deteriorated for rTMS03. This parameter cannot directly be linked to the effect of the intervention protocol as it was not measured as an outcome measure and the results are presented as exploratory observations. Several factors, including baseline fitness level and the level of spinal cord injury, could contribute to these differences between individuals. Muscle fatigue is also a contributing factor that may also explain the decline observed in rTMS03 cycling power.<sup>95</sup>

Findings of GRC scores show that two participants, rTMS01 and rTMS02, continuously reported functional improvements in their walking abilities and lower extremity function throughout the protocol; and rTMS03 initially reported no change in the mid-point and final assessment sessions but reported +3 score in the follow-up assessment session. These findings highlight the importance of capturing participants' subjective experiences, as they offer valuable insights that may not be fully reflected in statistical findings.

To sum up, the findings of this study show large variability between the two participants enrolled in the active treatment group. For rTMS02 the findings mostly align with the hypothesized outcomes while for rTMS03, the results do not support the hypothesis. While it is challenging to pinpoint the exact reasons why the combined intervention

benefited one participant more than the other, we can explore potential factors based on the observations and existing literature.

The improvements observed in participant rTMS02 highlight the potential benefits of pairing rTMS with FES cycling. In the previous literature on individuals who had experienced a stroke, it has been shown that rTMS can increase levels of participation and activity,<sup>96</sup> as well as enhance the effect of FES current in rehabilitation.<sup>97</sup> rTMS may have stimulated neuroplastic changes in the motor cortex of rTMS02, enhancing the brain's ability to learn and adapt movement patterns.<sup>98-100</sup> FES cycling, by providing targeted muscle activation and sensory input, could have further supported these neuroplastic changes and promoted motor learning, ultimately leading to improved function in this participant. Additionally, the intervention might have improved communication between the nervous system and muscles, leading to more efficient movement coordination.<sup>73</sup> While one participant (rTMS02) showed encouraging improvements, the other participant receiving the active treatment (rTMS03) did not experience similar gains and even showed declines in some tests which disconfirms the hypothesis. Several factors might have contributed to this outcome. First, this participant only completed eight out of the planned twelve intervention sessions. Studies on rTMS for SCI typically involve a longer duration, and missing sessions could have limited the cumulative effect needed for improvement. Second, this participant was 84 years old. While age is not necessarily a barrier to functional improvements with rehabilitation, the body's natural healing processes are slower in older individuals with iSCI. For example, it has been shown that older adults experience less improvement in their walking compared to younger individuals post injury.<sup>101</sup> Additionally, while neuroplasticity still occurs in older adults, it becomes dysregulated and destabilized with age, making it harder for the older brain to stabilize neural changes induced by interventions such as rTMS.<sup>102</sup> Additionally, this participant had a history of stroke predating his iSCI. While the lower extremity motor function was reported to return to baseline following this injury, a stroke can affect brain plasticity and potentially limit the effectiveness of rTMS.<sup>103</sup> Further research is needed to explore the use of rTMS in individuals with pre-existing neurological conditions. Third, this participant had a cervical level spinal cord injury, which typically affects a larger portion of the nervous system compared to lower spinal



cord injuries. This could present greater challenges in regaining function. Results of existing literature show the distance between the targeted muscle and the level of SCI can impact the efficacy of rTMS.<sup>104</sup> Specifically, when rTMS is applied to M1, the relative position of the motor neurons of the targeted muscle and whether they are located above or below the level of injury can influence the efficacy of the rTMS treatment. Comparing the cervical lesions to thoracic and lumbar, it has been shown that stimulating upper extremity muscles in a person with cervical lesion led to more prominent effects compared to lower extremity muscles.<sup>104</sup> More studies focusing on the effect of this protocol on people with different levels of injury are required to make definitive conclusions. Finally, this participant had a high sensitivity to rTMS initially, requiring a lower stimulation intensity for the first few sessions. Lower intensity stimulation may have reduced the effectiveness of the intervention. Overall, rTMS03's response could have been impacted by individual factors like comorbidities or injury characteristics. Moreover, the observed differences in outcomes between participants could be attributed to multiple factors, including baseline function, injury severity, and individual responsiveness to the intervention. It is worth mentioning that rTMS03 had a baseline WISCI-II score of 16 as opposed to rTMS02 score of 13 which could have played a role in the different outcomes of these two participants. In other words, there might be a greater potential for improvement in rTMS02 who started with lower baseline scores. This participant may have had more room for functional gains, whereas rTMS03 with higher initial scores may have already reached a plateau in his recovery, limiting the extent of further improvement. The sham participant, rTMS01, who received FES cycling with sham rTMS, also showed improvements in gait speed, TUG, and STS tests based on the limited available data. While definitive conclusions are difficult due to incomplete data, these improvements are expected as it has been shown that FES cycling leads to better performance on functional measures.<sup>105,106</sup> FES cycling can enhance performance on the TUG and STS tests by reducing spasticity and improving coordinated movements.<sup>106</sup> Since FES cycling activates the weakened and paralyzed muscles, another mechanism of improved motor function is an increase in muscle mass and therefore muscle strength.<sup>70</sup> Furthermore, FES cycling can induce neuroplasticity by producing repetitive movement and providing sensory feedback. This can facilitate activity-

dependent neuroplasticity and regulate the residual pathways reorganization below the level of injury.<sup>107</sup>

## 4.2 Comparison with Existing Literature

The study by Yang et al explored the effect of low-frequency rTMS combined with FES on hand function recovery in the stroke population.<sup>74</sup> This study divided patients into three groups, one receiving low-frequency rTMS, another receiving FES, and a third group receiving both treatments combined. Their results demonstrated that the combined rTMS and FES group showed significantly better improvements in the Total Active Movement (TAM) of fingers and Fugl-Meyer Assessment (FMA) scores compared to the groups receiving only one type of therapy. Similarly, in our study, we observed improvements in lower extremity function in one of the participants who received a combination of rTMS and FES cycling.

The study by Fawaz et al investigated the effects of FES combined with real versus sham rTMS on hand function in chronic iSCI.<sup>75</sup> Their randomized controlled trial included 22 participants divided into two groups, one receiving FES and real rTMS, and the other receiving FES and sham rTMS. Hand function and cortical excitability were assessed before and after the intervention. Their results showed that the group receiving real rTMS in addition to FES demonstrated statistically significant improvements in hand function tests (such as the action research arm test, modified Sollerman hand function test, nine-hole pegboard scale, and finger tapping test) compared to the sham rTMS group. This underscores the additional benefit of real rTMS therapy in enhancing hand function and motor recovery. In comparison, our findings align with the referenced study, as we also observed improvements in gait speed and functional tests in one of the participants receiving combined rTMS and FES cycling.

In a trial done by Krogh et al, 20 individuals with iSCI were randomized to receive either real or sham rTMS in addition to their usual care for four weeks.<sup>76</sup> Participants of this study received the stimulation over the M1 from Monday to Friday before receiving resistance training or physical therapy. LEMS and gait parameters including TUG were collected as outcome measures. Results of our trial, similar to Krogh's study show that

LEMS improved in rTMS02; however, this improvement did not reach the MCID in our trial. The TUG test results in Krogh's study show no significant improvement; however, in our study, rTMS02 experienced improvements in this test. Krogh's study reported more severe side effects, such as a seizure, facial muscle twitches, and tingling sensations in the scalp; these adverse events could be due to the stimulation intensity used in their protocol, which involved stimulation at 100% of RMT. On the contrary, we used a stimulation intensity of 90% of RMT which might have enabled a safer intensity and prevented adverse events such as seizures and facial twitches.

In another double-blind trial, Benito et al assessed LEMS, WISCI-II, and walking parameters such as step length, cadence, and TUG test in participants with iSCI who underwent a 15 daily session protocol.<sup>47</sup> Comparing our results to this study, we observed similar findings in LEMS, with improvements in the active group. The WISCI-II score remained unchanged in both studies. Benito's study also reported improvements in TUG, gait velocity, cadence, and step length in the active group. Our study showed improvements in gait velocity, cadence, and step length, although these results did not surpass the MCID. This discrepancy might be attributed to our smaller sample size and the longer duration of rTMS in Benito's study, which included 15 consecutive daily sessions. Based on the comparison with the results from Benito's study, it appears that employing a protocol with daily sessions could be more beneficial than our current protocol of bi-weekly sessions. Based on Benito's results increased frequency may enhance the effectiveness of the treatment and therefore, incorporating daily sessions into our protocol could potentially yield better outcomes by providing more consistent and sustained stimulation.

In conclusion, comparing the results of our trial to those of similar protocols reveals that our findings are largely consistent with previous studies, supporting the potential efficacy of combining rTMS with FES in a future trial which may enhance neuroplasticity and functional recovery more effectively than FES alone. This consistency across different motor functions (upper vs. lower extremities) and participant populations (stroke vs. SCI) strengthens the evidence base for incorporating rTMS into rehabilitation protocols. However, some observed differences in outcomes may be attributed to variations in the

specific protocols used, such as differences in rTMS frequency, intensity, duration, and the nature of the FES application. Our study confirms the findings of previous work by demonstrating the additional benefits of combining rTMS with FES in enhancing motor function.

### 4.3 Limitations

This case series had several limitations. First, the small sample size ( $n=3$ ) limits the generalizability of the findings of this study to a broader population of iSCI, especially considering all participants were male. Positively, there was representation from a wide age range and injury level, indicating that with larger sample sizes generalizability may increase. Second, data collection was incomplete for the sham participant who missed two assessments and two intervention sessions, which can interfere with the data interpretation and limit our discussion of the functional effects in the intervention group compared to the sham group. This limited the ability to distinguish the specific effects of rTMS combined with FES cycling from those of FES cycling alone, preventing a clearer understanding of the effects of each intervention individually. Furthermore, rTMS03 was not able to complete the intervention sessions as planned due to equipment issues; this impacted the consistency of the intervention delivery and outcome assessment. In addition, this participant received a low intensity stimulation for the first two intervention sessions due to high sensitivity which can limit the effectiveness. Finally, the duration of this protocol was 12 intervention sessions delivered twice a week over a period of six weeks. Our rationale for using this approach was to increase feasibility for participants, as we acknowledge individuals with iSCI have other appointments, occupations, and daily activities to participate in.

### 4.4 Clinical Implications

The findings in this thesis offer promising insights regarding pairing rTMS with FES cycling for individuals with iSCI, with potential clinical implications for rehabilitation. Participant rTMS02, who received the combined intervention of rTMS and FES cycling, demonstrated improvements in functional tests such as gait speed, cadence, TUG, STS, and LEMS. These improvements suggest that this intervention may have the potential to

promote neuroplastic changes and motor learning, leading to enhanced functional abilities in individuals with iSCI. Beyond these findings, the implications for clinical practice are significant. Integrating rTMS with FES cycling could enhance the known benefits of FES alone, providing a more effective rehabilitation strategy. This combined intervention could be implemented in clinical settings to optimize patient outcomes, offering a new standard of care for iSCI rehabilitation. Furthermore, the potential of rTMS to facilitate neuroplasticity opens up opportunities to explore its combination with other rehabilitation modalities. For instance, rTMS could be paired with gait training, functional training, or advanced robotic-assisted rehabilitation. These combinations could further amplify the therapeutic benefits, resulting in more comprehensive and effective treatment plans.

## 4.5 Future Direction

Future research should prioritize confirming the effects observed in this study through larger-scale investigations that address the limitations encountered. One crucial aspect is the small sample size, which necessitates studies with more participants to enhance the generalizability and validity of the findings. Based on the early results of this trial, younger adults with injury levels of thoracic and lumbar may be more likely to benefit from the effect of rTMS and FES cycling to improve lower extremity function; therefore, future studies should consider these factors in inclusion/exclusion criteria, participant matching, or sub-group analyses. It is recommended that future protocols employ intensities that are within the safety range and are tolerable by the participants. This could prevent further unwanted adverse events like headaches, facial twitches, and seizures. The intensity used in our trial (90% of RMT level) was shown to be safe in this regard. Moreover, based on the previous literature,<sup>47,48,76</sup> determining the optimal intervention protocol by adjusting the dosage, employing a protocol consisting of daily sessions, and increasing the frequency of sessions may play a role in further enhancing the effects of stimulation in exciting the motor cortex.

In addition to overcoming these methodological limitations, future studies can further explore several promising avenues. Investigating the effects of the intervention on other functional outcomes, such as the level of corticospinal excitability, could provide

valuable insights into the neurophysiological mechanisms underlying the observed functional improvements.

## 4.6 Conclusion

To summarize, the results of the current experiment indicated preliminary feasibility, acceptability, and safety of this innovative protocol in addition to potential improvements of lower extremity motor function for some individuals following iSCI. By addressing this trial's limitations, future studies can contribute significantly to advancing our understanding of the therapeutic potential of combining rTMS with FES for individuals with iSCI, ultimately leading to more effective and tailored interventions for improving motor function and quality of life in this population.

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# Appendices

## Appendix A: WREM Approval Letter



**Date:** 17 July 2023

**To:** Dr Janelle Unger

**Project ID:** 122650

**Review Reference:** 2023-122650-81465

**Study Title:** Exploring the effects of non-invasive brain stimulation paired with functional electrical stimulation to improve lower extremity function following incomplete spinal cord injury

**Application Type:** HSREB Initial Application

**Review Type:** Full Board

**Meeting Date:** 20/Jun/2023

**Date Approval Issued:** 17/Jul/2023

**REB Approval Expiry Date:** 17/Jul/2024

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Dear Dr Janelle Unger

The Western University Health Science Research Ethics Board (HSREB) has reviewed and approved the above mentioned study as described in the WREM application form, as of the HSREB Initial Approval Date noted above. This research study is to be conducted by the investigator noted above. **All other required institutional approvals and mandated training must also be obtained prior to the conduct of the study.**

### Documents Approved:

Document Name	Document Type	Document Date	Document Version
GRC	Paper Survey	27/Apr/2023	1
Data Collection Sheet	Other Data Collection Instruments	27/Apr/2023	1
First Assessment Session Form	Other Data Collection Instruments	27/Apr/2023	1
Follow-up Assessment Sessions Form	Other Data Collection Instruments	27/Apr/2023	1
Screening Form	Other Data Collection Instruments	27/Apr/2023	1
Poster - Clean	Recruitment Materials	26/Jun/2023	2
Protocol	Protocol	26/Jun/2023	2
Email Script - Recruitment - Clean	Recruitment Materials	26/Jun/2023	2
Email Script - Contact - Clean	Email Script	26/Jun/2023	2
Phone Script - Contact - Clean	Telephone Script	05/Jul/2023	3
Consent Form - Clean	Written Consent/Assent	05/Jul/2023	3

### Documents Acknowledged:

Document Name	Document Type	Document Date	Document Version
Study Budget	Study budget	27/Apr/2023	1

REB members involved in the research project do not participate in the review, discussion or decision.

The Western University HSREB operates in compliance with, and is constituted in accordance with, the requirements of the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2); the International Conference on Harmonisation Good Clinical Practice Consolidated Guideline (ICH GCP); Part C, Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations; Part 3 of the Medical Devices Regulations and the provisions of the Ontario Personal Health Information Protection Act (PHIPA 2004) and its applicable regulations. The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

Please do not hesitate to contact us if you have any questions.

Electronically signed by:

Ms. Jhananiee Subendran , Ethics Officer on behalf of Dr. Naveen Poonai, HSREB Chair, 17/Jul/2023 18:36

**Reason:** I am approving this document

*Note: This correspondence includes an electronic signature (validation and approval via an online system that is compliant with all regulations, See [Electronic System Compliance Review](#))*

**Appendix B: Lawson Approval Letter**

**LAWSON FINAL APPROVAL NOTICE**

**LAWSON APPROVAL NUMBER: R-23-345**

PROJECT TITLE: Exploring the effects of non-invasive brain stimulation paired with functional electrical stimulation to improve lower extremity function following incomplete spinal cord injury

PRINCIPAL INVESTIGATOR: Dr Janelle Unger

LAWSON APPROVAL DATE: 25/07/2023

ReDA ID: 13312

Overall Study Status: Active

Please be advised that the above project was reviewed by Lawson Administration and the project was **approved**.

All research must follow applicable laws, regulations, policies, procedures and guidance, including hospital and Lawson policies, and Lawson Standard Operating Procedures.

**Please provide your Lawson Approval Number (R# above) to the appropriate contact(s) in supporting departments (e.g. Lab Services, Diagnostic Imaging, etc.) to inform them that your study is starting. The Lawson Approval Number must be provided each time services are requested.**

Dr. David Hill

Scientific Director and Integrated V.P. Research

Lawson Health Research Institute

## **Appendix C: Letter of Information and Consent**

### **Letter of Information**

#### **Project Title**

Exploring the effects of non-invasive brain stimulation paired with functional electrical stimulation to improve lower extremity function following incomplete spinal cord injury.

#### **Document Title**

Letter of Information and Consent – Participant

#### **Principal Investigator**

Janelle Unger, PhD, PT

#### **Additional Research Staff**

Fereshteh Ghahremani, BSc, PT

#### **1. Sponsor/Funder Information**

This study is funded by Western University through the “Western Strategic Plan for Canadian Institute of Health Research (CIHR) Success Program” grant.

#### **2. Conflict of Interest**

The researchers have an interest in completing this study. Their interest should not affect your decision to participate in this study.

#### **3. Invitation to Participate**

We would like to invite you to participate in this study because you are affected by incomplete Spinal Cord Injury (iSCI). Please read this document fully before deciding to participate. You are able to contact the researchers of this study at any time and ask any questions you might have about the process. All of your concerns should be addressed before participating in this project. Please feel free to consult any other person you wish such as your friends, family members, and employer. Participating in this study is voluntary.

#### **4. Why is this study being done?**

The purpose of this study is to investigate a more effective method for helping people who are affected by iSCI to gain leg function and improve in walking, balance, and muscle strength. The combination of two interventions that do not require any incision or puncture, will be used in this study to explore whether it shows more effectiveness compared to each of those interventions alone. These interventions are repetitive Transcranial Magnetic Stimulation (rTMS) and Functional Electrical Stimulation (FES) Cycling. rTMS is a non-invasive procedure that uses magnetic pulses to stimulate specific areas of the brain. It's like using a magnet to gently activate certain parts of your brain to help with muscle strengthening. The magnetic pulses create small electric currents in your brain, which can affect how it functions. rTMS has shown promise as a treatment option and is generally safe. Overall, it's a way to use magnets to influence your brain activity and potentially improve your mobility. Moreover, FES cycling is a technique that uses small electrical currents to make your leg muscles move while you cycle. It's like getting a gentle electrical push to help your legs pedal even if you have difficulty moving them on your own. This can be useful for people with conditions like paralysis or nerve damage. FES cycling helps improve muscle strength, coordination, and overall fitness by giving your legs a workout. It's a way to exercise and keep your muscles active even if you can not move them as easily as you would like.

#### **5. How long will you be in this study?**

There will be 12 study visits during your participation in a period of 6 weeks (2 sessions per week) along with 4 assessment sessions. Assessment sessions will be held in first, third, and last week and will be held on different days than treatment sessions. One additional final assessment session will take place two weeks after the final treatment session; therefore, it is expected that you will be in the study for 8 weeks. Each treatment session will last approximately 90 minutes and each assessment session will last approximately 60 minutes. We aim to recruit 14 participants for this study.



## **6. What will happen during this study?**

If you decide to participate in this study, then you will be assigned to one of the two groups described below randomly. Randomization means that you are put into a group by chance (like flipping a coin). There is no way to predict which group you will be assigned to. You will have an equal 50/50 chance of being placed in either group. Neither you nor the assessors will be aware of which group you are assigned to. There will be two groups in this study; one group is the intervention group which will receive real rTMS with FES Cycling and the other is the control group which will receive sham rTMS with FES Cycling. Sham rTMS is a non-active, placebo-like version of the rTMS and participants in the control group will receive a similar procedure without the magnetic stimulation.

You are eligible to participate in this study if you are diagnosed with iSCI and you are at least one year post-diagnosis; you should be able to walk independently for 10 meters without the help of other individuals. If you have any other orthopedic or neurological implications that affect your lower limb function, you will be excluded from the study; additionally, if you have brain implants or pacemakers in your heart or any metal pieces in any part of your body, you are epileptic, you have received rTMS before, or you are pregnant, you will be excluded from the study.

## **7. What are the study procedures?**

If you agree to participate you will be asked to:

- Participate in 12 treatment sessions in which you will spend the first 30 minutes receiving the real or sham rTMS and the next 60 minutes on the FES bikes.
- Participate in 4 assessment sessions in which various tests like your walking speed and muscle strength and other functional tests (e.g., Timed Up and Go test, sit-to-stand test) will be performed and your data will be collected.
- Fill out a questionnaire in each assessment session.
- Participate in the study in person at Parkwood Hospital.

The study procedure will be as follows:

<b>Week #</b>	<b>Session #</b>	<b>Procedure</b>
1	Assessment 1	<ul style="list-style-type: none"> <li>• Willingness to participate questionnaire</li> <li>• Gait mat walk</li> <li>• Sit-to-Stand test</li> <li>• Timed-Up-and-Go test</li> <li>• Postural sway test (eyes open &amp; eyes closed)</li> <li>• Muscle strength grading</li> </ul>
1-3	Treatment 1-6	<ul style="list-style-type: none"> <li>• Recording Resting Motor Threshold</li> <li>• 40 minutes rTMS</li> <li>• 60 minutes FES cycling</li> </ul>
3	Assessment 2	<ul style="list-style-type: none"> <li>• Gait mat walk</li> <li>• Sit-to-Stand test</li> <li>• Timed-Up-and-Go test</li> <li>• Postural sway test (eyes open &amp; eyes closed)</li> <li>• Muscle strength grading</li> <li>• Rating improvement questionnaire</li> </ul>
4-6	Treatment 7-12	<ul style="list-style-type: none"> <li>• 40 minutes rTMS</li> <li>• 60 minutes FES cycling</li> </ul>
6	Assessment 3	<ul style="list-style-type: none"> <li>• Gait mat walk</li> <li>• Sit-to-Stand test</li> <li>• Timed-Up-and-Go test</li> <li>• Postural sway test (eyes open &amp; eyes closed)</li> <li>• Muscle strength grading</li> <li>• Rating improvement questionnaire</li> </ul>
8	Assessment 4	<ul style="list-style-type: none"> <li>• Gait mat walk</li> </ul>

		<ul style="list-style-type: none"> <li>• Sit-to-Stand test</li> <li>• Timed-Up-and-Go test</li> <li>• Postural sway test (eyes open &amp; eyes closed)</li> <li>• Muscle strength grading</li> <li>• Rating improvement questionnaire</li> </ul>
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Experimental Procedures:

The following tests are considered experimental and will only be done for participants of this study:

- Walking speed: You will be asked to walk on a gait mat back and forth to provide data.
- Walking Index for Spinal Cord Injury (WISCI) II: This test is done at the same time as the Walking Speed test. A physiotherapist will collect data about your walking patterns while you are walking on the gate mat.
- Sit-to-Stand: You will be asked to wear 6 sensors on 6 joints of your body including 2 on your wrists, 2 on your ankles, 1 on your sternum, and 1 on your lower back and perform a Sit-to-Stand test from a chair 3 times and your data will be collected.
- Timed-Up-and-Go test: You will be asked to wear the same sensors mentioned in the previous test and then walk on a flat surface for 3 meters.
- Postural Sway Test: You will be asked to wear the same sensors as before and stand still with your eyes open for 1 minute and closed for the next part to test your balance.
- Lower Extremity Motor Score (LEMS): A physiotherapist will measure the strength of your lower limb muscles by asking you to do a movement against resistance.

### Questionnaires:

- You will be provided with a questionnaire at each assessment session except the first one (3 times), and you will be asked to rate your recovery in each assessment session. This questionnaire will take 1 minute to answer. In addition, in the final assessment session, you will be asked to fill out a questionnaire regarding your blinding perception which will take 1 minute to complete.

### **8. What are the risks and harms of participating in this study?**

The risks of participating in this study are rare; side effects associated with rTMS might include (the numbers in parentheses show how often these side effects happen):

- Scalp discomfort and pain, headaches, light-headedness, dizziness, and spasms or twitching of facial muscles, are common (20-30%). You may be recommended to take a pain medicine available without a prescription before the procedure.
- Persistent headaches, fatigue, and fainting (1-7%). In case of these side effects, adjustments will be made to the level of stimulation to reduce the symptoms.
- Emotional high (mania) in people with bipolar disorders (less than 1%). There will be more precautions considered for those participants who are diagnosed with this disorder.
- Seizures (less than 0.03%); appropriate medical guidelines will be followed in case of a seizure incident.

Risks and side effects associated with FES Cycling include:

- Skin irritations or discomfort in the place of electrodes.
- Muscle soreness and fatigue and joint pain or injury.
- Cardiovascular strain
- Autonomic dysreflexia

In order to address these side effects, researchers will adapt the treatment parameters such as intensity and duration of the exercise to minimize the potential risks. In addition, participants will be monitored closely, and appropriate medical care will be provided if required. Minor side effects such as skin irritation or muscle soreness should disappear

within a few days following the sessions; if they persist, it is required to alert the research team.

**9. What are the benefits of participating in this study?**

Participation in this study may have some physical benefits, as we hope these treatments will improve walking speed and coordination, muscle strength, and general lower limb function. By participating in this study, you will be helping to expand knowledge in this field and potentially help others with iSCI.

**10. Can participants choose to leave the study?**

Participants have the right to withdraw from this study at any time. If you decide to withdraw from the study, you have the right to request (e.g., by phone, in writing, etc.) withdrawal of information collected about you. If you wish to have your information removed, please let the researchers know and your information will be destroyed from our records. Once the study has been published, we will not be able to withdraw your information.

**11. How will participants' information be kept confidential?**

In case you decide to participate in the study, researchers will collect some personal health information; this information includes your name, age, sex, gender, details about your injury, and contact information (email address, phone number). All of the electronic data collected from you will be saved through the secure servers of the hospital. The researchers will keep all personal information about you in a secure and confidential location for 15 years. All of the printed materials and data will be stored in a secure, locked place which only members of the research team will have access to. Your name will not be associated directly with the data collected about you; instead, you will be assigned a study number that will be used for identifying your data. All the documents linking your name to your study number will be stored in a secure location separate from the rest of the study data. The principal investigator and study members including researchers, representatives of the Western Health Sciences Research Ethics Board (HSREB), and representatives of the Lawson Quality Assurance Education Program (QAEP) will have access to your data.

**12. Are participants compensated to be in this study?**

Participation in this study does not pose any costs except parking and transportation, for which the participants will be compensated in the amount of \$15.00 per study visit.

**13. What are the rights of participants?**

You have the right to decide to whether participate in the study or not; participation is completely voluntary. Even if you consent to participate you have the right to not answer individual questions or to withdraw from the study at any time, without any penalty or negative consequences on your normal treatment routine; you will be informed about the process of withdrawing and what will happen to the data collected about you. You do not waive any legal right by consenting to this study.

**14. Whom do participants contact for questions?**

If you have any questions, concerns, or need to know more about the study, feel free to contact the principal investigator of the study: Janelle Unger.

**This letter is yours to keep for future reference.**

## Consent

### 1. Project Title

Exploring the effects of non-invasive brain stimulation paired with functional electrical stimulation to improve lower extremity function following incomplete spinal cord injury.

### 2. Document Title

Letter of Information and Consent – Participant

### 3. Principal Investigator

Janelle Unger, PhD, PT

### 4. Additional Research Staff

Fereshteh Ghahremani, BSc, PT

I have read the Letter of Information, have had the nature of the study explained to me, and I agree to participate. All questions have been answered to my satisfaction.

\_\_\_\_\_

Print Name of Participant	Signature	Date
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My signature means that I have explained the study to the participant named above. I have answered all the questions.

\_\_\_\_\_

Print Name of Person Obtaining Consent	Signature	Date
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**Appendix D:** Screening Form (containing questions regarding contraindications of rTMS and FES cycling)

**Screening Form**

Date: \_\_\_\_\_

**Demographic Data:**

Participant ID: \_\_\_\_\_ Age: \_\_\_\_\_

Sex: \_\_\_\_\_ Gender: \_\_\_\_\_

Level of injury: \_\_\_\_\_ ASIA score: \_\_\_\_\_

Mechanism of injury:       Traumatic       Non-traumatic

- Are you at least one year post injury/diagnosis?       Yes       No
- Do you have non-progressive SCI?       Yes       No
- Are you able to walk independently without the help of another person for 10 meters?       Yes       No
- Do you have other orthopedic or neurological disorders that affect your lower limb function?       Yes       No

**TMS Contraindications:**

- Do you have epilepsy, or have you ever had a convulsion or a seizure?       Yes       No
- Have you ever had a fainting spell or syncope?  
If yes, please describe on which occasion(s).       Yes       No

\_\_\_\_\_  
\_\_\_\_\_

- Have you ever had severe (i.e., followed by loss of consciousness) head trauma?       Yes       No



- Do you have any hearing problems or ringing in your ears?  Yes  No
  - Are you pregnant or is there any chance that you might be?  Yes  No
  - Do you have metal in the brain/skull (except titanium)?  
(e.g., splinters, fragments, clips, etc.)  Yes  No
  - Do you have cochlear implants?  Yes  No
  - Do you have an implanted neurostimulator?  
(e.g., DBS, epidural/subdural, VNS)  Yes  No
  - Do you have a cardiac pacemaker, intracardiac lines,  
or metal in your body?  Yes  No
  - Do you have a medication infusion device?  Yes  No
  - Are you taking any medications? (Please list)  Yes  No
- 

- Did you ever have surgical procedure on your spinal cord?  Yes  No
- Do you have spinal or ventricular derivations?  Yes  No
- Did you ever undergo TMS in the past?  Yes  No
- Did you ever undergo an MRI in the past?  Yes  No

**FES Contraindications:**

- Do you have implanted electronic devices in your body?  Yes  No
- Do you have unhealed bone fractures?  Yes  No
- Do you have severe contractures in your lower limb?  Yes  No
- Do you have extreme osteoporosis?  Yes  No
- Do you have extreme osteoarthritis?  Yes  No

## **Appendix E: Willingness to Participate Questionnaire**

### **Willingness to Participate**

Please rate your willingness to participate in this protocol based on the options below:

- 0: Not willing at all
- 1: Minimally willing
- 2: Slightly willing
- 3: Moderately willing
- 4: Considerably willing
- 5: Willing
- 6: Very willing
- 7: Highly willing
- 8: Exceptionally willing
- 9: Completely willing
- 10: Absolutely willing

# Curriculum Vitae

**Name:** Fereshteh Ghahremani

**Post-secondary  
Education and  
Degrees:** University of Social Welfare and Rehabilitation Sciences  
Tehran, Iran  
BSc of Physiotherapy, 2018-2022

The University of Western Ontario  
London, Ontario, Canada  
MSc of Health and Rehabilitation Sciences – Field of  
Physiotherapy, 2022-2024

**Honours and  
Awards:** Siskinds Studentship in Spinal Cord Injury from St. Joseph’s  
Health Care Foundation  
October 2023

Western Graduate Research Scholarship from the University of  
Western Ontario  
Winter 2024

Second Best Overall Poster Presentation, Parkwood Institute  
Research (PIR) Research Day  
May 2024

Scholarship for MSc of Physiotherapy without an Entrance Exam  
from the University of Social Welfare and Rehabilitation Sciences  
Summer 2022

Tuition Fee Scholarship for BSc of Physiotherapy from University of Social Welfare and Rehabilitation Sciences

2018-2022

Ranked 1<sup>st</sup> among 27 Students in the Class of Physiotherapy 2018, University of Social Welfare and Rehabilitation Sciences

2018-2022

**Related Work  
Experience**

Graduate Teaching Assistant

The University of Western Ontario

2022-2024

Graduate Student Assistant

The University of Western Ontario

2024

**Presentations:**

London Health Research Day, London, ON

Poster Presentation

June 2023

Parkwood Institute Research (PIR) Research Day, London, ON

Poster Presentation

May 2024

World Congress of Neurorehabilitation (WCNR), Vancouver, BC

Poster Presentation

May 2024