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Study Title: Enhancement of motor function after spinal cord injury.

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Brief Description

Motor function is largely disrupted in veterans with spinal cord injury (SCI). This has tremendous impact in daily-life activities. This study will examine physiological changes in pathways controlling motor function after SCI and novel methods to enhance the recovery of upper and lower extremity motor function by combining non-invasive repetitive brain stimulation with motor training. The repetitive brain stimulation will occur using a wire coil placed over the participants' head. When activated, this coil will generate a magnetic pulse over a specified area of the head. During training, we will monitor muscle activity through the use of surface electrodes. Subjects will perform precision grip and wrist movements. Impairment in hand function is a major problem after stroke, amyotrophic lateral sclerosis, multiple sclerosis, and other motor disorders, therefore, our work may also be relevant for individuals with other lesions of the nervous system.

Objectives: The goals of this study are to examine the physiology of Central Nervous System pathways contributing to the control of upper and lower extremity movements after SCI, and to promote the recovery of extremity movements by using non-invasive brain stimulation and motor training.

A. Specific Aims and Hypothesis:

Aim 1. Neural Control of Movements in SCI and Control Subjects

Investigate physiological mechanisms contributing to the control of hand movements.

Aim 2. Enhance recovery of motor function by using non-invasive repetitive transcranial magnetic stimulation (rTMS)

To accomplish this aim we propose to complete two main experiments. First we will use rTMS to test the hypothesis that *rTMS induced cortical plasticity during movement will enhance voluntary output in hand muscles (as measures by electromyography and Jebsen Taylor Test) after spinal cord injury (Aim 2a).* Second, we will combine precision grip and wrist training with rTMS to test the hypothesis that *precision grip training outcomes will be enhanced by rTMS induced cortical plasticity (aim 2b).*

B. Background and Significance to the VA Mission

Deficits in motor function are one of the most devastating functional impairments affecting individuals with SCI because of the tremendous impact in daily-life functions such as eating, grasping, writing, and many others (Snoek et al., 2004; Herrmann et al., 2010). This has important socio-economic implications that are a significant drive towards the development of treatments for the recovery of motor function. Although a number of studies have reported the beneficial effects of hand motor training after cervical SCI the overall improvements remain limited (for review see Spooren et al., 2009). Therefore, there is a need to develop novel mechanistic-driven therapeutic interventions to enhance hand motor function of individuals with chronic SCI.

Neural Control of Movements in SCI and Control Subjects (Aim 1): Animal studies have demonstrated that the motor cortex is involved in the control of hand actions including a precision grip and wrist movements through a selective activation of the corticospinal tract (Lemon, 2008). In agreement, human studies using functional magnetic resonance imaging have shown activity-dependent changes in BOLD signal activity in both motor cortices during a precision grip involving fingers and a wrist task (Ehrsson et al., 2000; Sehm et al., 2010). Studies using TMS have shown an increase in corticospinal drive targeting finger and wrist muscles during a similar motor task (Perez and Cohen, 2008, 2009a). The sizes of motor evoked potentials (MEPs) elicited by TMS in a finger muscle were larger during a precision compared to a power grip force (Schieppati et al., 1996; Tinazzi et al., 2003). It has been proposed that the increase in corticospinal excitability is, at least in part, related to a cortical mechanism since intracortical and interhemispheric inhibition were decreased and H-reflexes remained unchanged during this motor task (Schieppati et al., 1996; Tinazzi et al., 2003). Together, these data highlight the contribution of the motor cortex and corticospinal drive to the control of hand movements in humans. After cervical SCI, the number of corticospinal projections and voluntary drive to affected muscles is reduced. At rest, there have been multiple demonstrations of corticospinal reorganization after SCI (Levy et al., 1990; Bruehlmeier et al., 1998; Ellaway et al., 2007) but little is known about motor cortical and corticospinal reorganization during the remaining hand voluntary activity. This is a critical issue for elucidating the role of the corticospinal tract in motor recovery and rehabilitation strategies after SCI.

Effects of rTMS on motor function and corticospinal plasticity (Aim 2a): Previous evidence has demonstrated that neurorehabilitation programs can improve motor outcomes by enhancing reorganization in the corticospinal pathway (Nudo, 2003).

Impact of combining rTMS with motor training (Aim 2b): Motor training strategies used in individuals with cervical SCI often focus on increasing volitional arm muscle activation through strength training, electrical stimulation, and general exercises (see Spooren et al., 2009). While these studies reported that motor training enhances hand motor function, behavioral improvements remain limited. Over the last decades, high frequency rTMS applied over the motor cortex has been shown to induce changes in motor cortical excitability (see section above). Since the mechanisms underlying these effects are related to CNS plasticity, rTMS has been combined with motor training as a tool for enhancing motor function in individuals with movement disorders.

Impairment in motor function is a major deficit in veterans with spinal cord injury (SCI). While rehabilitative interventions have shown success in improving aspects of hand motor function their overall effects remain limited. The goals of this study are to examine the physiology of nervous system pathways contributing to the control of movements after cervical SCI, and to promote the recovery of upper and lower extremity movements by using non-invasive brain stimulation and motor training. We focus on both hand and arm function, which are necessary for most of our daily-life activities, as well as lower extremity movement; therefore, our results may directly impact the quality of life for veterans and their caregivers by enhancing their independence and level of care.

C. Study Design

This study will focus on two basic aspects involved in upper and lower extremity motor function, and how these are affected after chronic SCI using a randomized sham control design with single blind.

Methodology:

This study will consist of electromyography (surface and intramuscular), peripheral nerve stimulation, and transcranial magnetic stimulation, electrical stimulation, of the hand, arm, leg, and foot representation of the primary motor cortex, as well as MRI scans of the brain. We will examine the physiological measurements of upper and lower extremity muscles (such as in the first dorsal interosseous (FDI), biceps brachii (BIC), anterior deltoid (AD), tibialis anterior (TA), hamstring (HAMS) and quadriceps (QUAD)). This study may occur at the Miami Project to cure Paralysis at the University of Miami. We will include subjects between the ages of 18 and 85, both healthy controls and individuals with chronic spinal cord injuries that occurred at least 6 months prior to recruitment. Both healthy controls and those with spinal cord injuries will be able to perform small hand and arm movements and small leg and foot movements. The primary outcome measures of this study are muscle responses to stimulation with magnetic pulses using TMS and electrical stimulation of a peripheral nerve in the arm or leg. We propose to enhance the recovery of motor function by using new protocols of high frequency non-invasive repetitive TMS (rTMS) and motor training. Repetitive TMS will be used during hand, arm, leg and foot movements in a task-dependent manner to induce cortical plasticity and enhance voluntary output of the muscles associated with those movements. Second, rTMS will be applied in a task-dependent manner during a visuo-motor training task that also involves movements of the hands, arms, legs or feet.

Phase 1

Aim 1. Neural Control of Movements in SCI and Control Subjects

We will use TMS, CMEPS, and peripheral nerve stimulation to test the hypotheses that 'precision grip and wrist movements will be associated with reduced motor cortical (as measured by intracortical inhibition) and spinal inputs (as measured by F-wave persistence and amplitude) to hand and wrist motoneurons after cervical SCI compared to controls'. Subjects will be instructed to perform a precision grip (between index and thumb) and simultaneously wrist flexion or extension movements. Measurements of cortical and motoneuronal excitability will be acquired during movement.

Each testing session will be separated by at least two days. Subjects will be instructed to perform a precision grip (between index and thumb) and simultaneously wrist flexion or extension movements. Measurements of cortical and motoneuronal excitability will be acquired during movement. Tasks involving lower-limb movement will also be tested as control tasks. In each session, we will use the following experimental setup and motor tasks:

Experimental setup – During testing, individuals will be seated in an armchair with both elbows flexed at 90°. Each arm will be supported by a custom device attached to a potentiometer to measure wrist flexion and extension angles and a load cell to measure grip forces. Index fingers and thumbs will be positioned in a customized gripping tube attached to a two-axis load cell. Subjects who cannot be transferred will be tested in their wheelchair by using customized platforms that we previously used in individuals with SCI. Surface electrodes will be positioned bilaterally on the skin overlying upper and lower-limb muscles in a bipolar montage (inter-electrode distance approximately 2 cm). The amplified EMG signals will be filtered, sampled, and stored for analysis. Forces will be measured by load cells and angles by potentiometers and stored for analysis.

Motor task – In a first test, subjects will be instructed to perform full wrist flexion and simultaneously perform a precision grip (between index and thumb) with one hand. In a second test, subjects will be instructed to perform full wrist extension and a precision grip with one hand. At the start of testing,

individuals will perform 3 brief precision grip maximum voluntary contractions (MVCs) (3–5 s) and wrist flexion and extension MVC with 30 seconds of rest. Custom software will be used to acquire signals from potentiometers and load cells to display visual feedback corresponding to wrist flexion and extension angles and 10% of MVC grip force. Subjects will be instructed to move a cursor at a comfortable speed and to hold the cursor in the target force and position for 2-4 seconds. During lower-limb tasks subjects will be instructed to move as cursor by performing ankle dorsiflexion and plantar flexion movements. Approximately thirty repetitions of each task will be randomly tested.

During these motor tasks we will examine: (A) TMS measurements and (B) motoneuronal excitability in the first dorsal interosseous, and flexor and extensor carpis radialis muscles. TMS and peripheral nerve stimulation pulses will be delivered when subjects reach a certain degree of wrist flexion or extension and a certain percentage of MVC in the precision grip. Stimulation will be triggered if both goals are reached. This window in both directions will be modified for individuals who showed more difficulties in performing the movement in either direction.

(A) TMS measurements- Transcranial magnetic stimuli will be delivered from a stimulator through a figure-eight coil. TMS will be delivered to the optimal scalp position for activation of the left or right first dorsal interosseous, and flexor and extensor carpis radialis muscles. The TMS coil will be held to the head of the subject with a custom coil holder while the head is firmly secured to a headrest by straps to limit head movements. TMS measurements during precision grip and wrist movements will include the following:

MEPs – Resting and active motor thresholds (RMT and AMT) will be tested in each of the muscles. For this testing, TMS intensity will be adjusted to produce an MEP of 50% of the maximal MEP on each muscle tested. 30 MEPs will be average in each condition. Cervicomedullary Motor Evoked Potentials (CMEPs): Supramaximal electrical stimulation will be administered posterior to the mastoid process to ellicit motor evoked potentials to upper and lower limb muscles.

Short-interval intracortical inhibition (SICI) – A conditioning stimulus (CS) will be set at an intensity of 70% of AMT. The test stimulus (TS) will be adjusted to produce an MEP of 50% of MEP-max. Test stimuli will be delivered 2.5 ms after CS. 25 TS and CS will be averaged in each condition.

Interhemispheric inhibition (IHI) – A supra-threshold CS will be set at an intensity above the RMT and given 10-50 ms before a TS delivered to the contralateral motor cortex. The coils will be positioned at the optimal location for activating the muscle tested and attached to coil holders.

(B). Motoneuronal excitability (reflected by F-wave persistence and amplitude): F-waves will be tested by using supra-maximum stimulus intensity (120% of the maximal motor response)to the ulnar nerve at the wrist and the median nerve at the elbow. The anode and cathode will be approximately 3 cm apart and 1 cm in diameter. We will examine F-waves in first dorsal interosseous, flexor and extensor carpis radialis muscles.

Phase 2

Aim 2a. Enhance recovery of motor function by using non-invasive repetitive transcranial magnetic stimulation (rTMS)

To accomplish this aim we propose to complete two main experiments. First we will use rTMS to test the hypothesis that *rTMS induced cortical plasticity during movement will enhance voluntary output in hand muscles (as measures by electromyography and Jebsen Taylor Test) after spinal cord injury (Aim 2a).* Second, we will combine precision grip and wrist training with rTMS to test the hypothesis that *precision grip training outcomes will be enhanced by rTMS induced cortical plasticity (aim 2b).*

Experiment 1 (Aim 2a)

Participants will be randomly assigned to three groups: (1) rTMS, (2) Sham rTMS and (3) sham rTMS over control brain area. Randomization will be performed by lottery (i.e. Drawing from an envelope a piece of paper indicating the intervention). In the first two groups, rTMS stimulation will be targeting finger and wrist muscles during precision grip and write voluntary contractions. In the last group, rTMS will be applies over the dorsolateral prefrontal cortex (DLPFC) or at the leg presentation of the primary motor cortex, or at other related control area as needed. Each subject will be asked to participate in all sessions separated by a washout period of approximately one week. During testing, subjects will be seated in an armchair with both arms flexed at the elbow by 90 degrees. In each group we will used the same apparatus described in Aim1. At the start of the experiment subjects will perform 3 brief MVCs (3-5s) into index finer abduction and writs flexion and extension, separated by 30 seconds. The maximal forces will be sued to set targets for subsequent submaximal contractions.

rTMS protocol- rTMS will be applied by a magnetic stimulator through a figure of eight coil with the same coil position as in Aim1. rTMS will consist of a total of 1200 pulses at an intensity of 80% of the AMT applied during a precision grip. At each time three targets will be presented on a computer screen. Each target will indicate a GO signal to compete a precision grip. During each precision grip 5 pulses at 5Hz will be applies. In total, 8 blocks of 10 trains of 15 pulses at 5Hz separated by inter train interval of 10s will be applied (1200 pulses). Each block will be separated by 30s of rest. The periods of stimulation will last approximately 24 minutes.

Measurements before and after rTMS protocol- We will examine: (a) MEPs, SICI, and F-waves (see procedures in AIM1), and (b) EMG and force output. Before rTMS, to examine EMG and force output individuals will receive visual feedback on a computer screen corresponding to 10% of MVC during a precision grip. The target will be presented for 1 second and then it will disappear at intervals of 5-6 seconds. Subjects will be instructed to reach the target as accurately as possible without making any corrections. Three sets of 20 repetitions will be tested. Signals will be acquired and the mean of force displacement plus 1 standard deviation (SD) will be calculated. After rTMS, subjects will not be told whether the visual feedback is derived from their actual or from their previous performance. Then, the visual feedback presented in the computer screen will correspond to mean forces +1SD values exerted prior rTMS.

The Jebsen Taylor Hand Function Test

The JHFT was developed to provide a standardized and objective evaluation of several major aspects of hand function using simulated activities of daily living.
(Jebsen et al. 1969)

The Jebsen Taylor Hand Function Test is a standardized test with high intra-tester ($r = 0.85$; $p > 0.05$) and inter-tester reliability (intraclass correlation coefficient ranging from 0.82 to 1.00). It is designed for adults with neurological or musculo-skeletal conditions involving hand disabilities. The test items include a range of fine motor, weighted and non-weighted hand function activities: (i) writing (copying) a

sentence, (ii) turning over 3 × 5 cards, (iii) picking up small common objects such as a paper clip, bottle cap and coin, (iv) simulated feeding using a teaspoon and 5 kidney beans, (v) stacking checkers, (vi) picking up large light objects (empty tin cans), and (vii) picking up large heavy objects (0.5 kg tin cans). The time to complete each task was recorded in seconds. The affected hand was tested first. Subjects were allowed a maximum of 180 s to complete each sub-test. If the subject could not complete the task within the time allowed, 180 s was taken as the completion time to avoid fatigue (109).

ASIA examination

- ASIA 2002; Marino et al., 2003

•Pin prick with a safety pin and light touch with a cotton ball are tested. For pinprick the result is graded as 2- normal; 1- impaired where difference between sharp and dull is appreciated but less; 0- difference could not be appreciated between sharp and dull. For light touch 2- reports when touched and feels the same as face 1- reports touched but less than in face 0-does not reliably report being touched

•The dermatomes tested are C2 - occipital protruberance behind the ear C3 - supraclavicular fossa C4 - AC joint apex (C4 may extend down the chest almost to the nipple line) C5 - lateral antecubital fossa C6 - dorsal surface of proximal phalanx of thumb C7 - dorsal surface of proximal phalanx of middle finger C8 - dorsal surface of proximal phalanx of little finger T1- medial antecubital fossa T2- axilla apex T4- nipple liine T6 - xiphisternum T10 - umbilicus T12 - inguinal ligament midline L1,23 - thigh L4- medial malleolus L5 - dorsum of foot at 3rd MTP joint S1- lateral heel S2- popliteal fossa S3- ischial tuberosity S4,5 - perianal region

•Optional sensations that can be tested are joint movement (reported as absent, impaired - correct in 8/10 of large joint movements only or normal-correct 8/10 of large and small movements both) , deep pressure sensation (reported as present or absent)

Electrical Perceptual Threshold

The EPT method uses incrementing electrical stimulation and the method of limits to determine sensory threshold. (Ellaway and Catley 2013; Macklin and Perez et al, 2015).

Chedoke Arm and Hand Activity Inventory

The purpose of this is to evaluate the functional ability of the hemiplegic arm and hand to perform tasks. The performance of the affected limb is scored using a 7 point activity scale ranging from total assistance to complete independence.

Lower Extremity Physiological Examination Components:

Range of Motion (ROM): active ankle and hip ROM will be measured by a motion capture system (Opti Track, V120: Tri camera, NaturalPoint, Inc) in sitting and standing position. In sitting, subjects will be instructed to complete maximal voluntary dorsiflexion for 10 times separated for period of 10 sec of rest. In standing, subjects will be instructed to complete maximal voluntary hip flexion for 10 times separated for period of 10 sec of rest. Trunk movements will be avoided during testing. The motion capture system will also be utilized to measure foot drop and hip flexion. Markers will be positioned on the external line of the mid trunk, hip, knee, external malleolus, and the lateral side of the 5th metatarsophalangeal joint. The elevation of the toe above ground level will be taken as a measure of foot drop. The amplitude of toe elevation will be calculated from the distance between the marker placed on the 5th metatarsophalangeal joint and the ground (Barthélemy et al., 2010). The largest distance between these two points will be determined and will be referred to as the highest toe elevation. The presence or absence of the second toe elevation prior to heel strike will measured by subtracting the excursion of the malleolus marker from the elevation of the toe. Hip angle will be constructed by using the trunk, hip and knee markers.

Pinch Grip Strength:
Will be assessed bilaterally using load cells that will record the force generated by the subject. Force will be applied by the thumb and index finger and will be recorded in Newtons (N).

Modified Ashworth Scale and Pendulum Test:
Will be used to measure spasticity level in subjects with SCI during soft tissue stretching.
(Modified Ashworth Scale; Bohannon and Smith, 1987)

Phase 3

Experiment 2 (Aim 2b) :

Individuals with SCI and healthy controls will be randomly assigned to two groups: (1) training + rTMS, and (2) training + sham rTMS. Randomization will be the same as describes above. Training will be complete in approximately 15 sessions over approximately 3 weeks. In each session, stimulation or sham stimulation (approximately 25 minutes) will be applied during precision grip and wrist visuo-motor training (approximately 1 hour).

Training + rTMS group- Training will consist of executing three different grip forces with one hand and simultaneously wrist flexion and extension movements while the contralateral hand is at rest.

Subjects will be instructed to follow a target line on a computer screen as accurately as possible while performing precision grips with simultaneously maximal wrist flexion and extension. Stimulation will be triggered if both movements are performed. See Experiment 1 for rTMS parameters. At each time three targets will be presented separated by approximately 2 seconds of reset on the screen for a total duration of 10 seconds. The period of stimulation will last approximately 24 minutes. Subjects will be randomly assigned to two groups: training + rTMS, and training + sham rTMS. A train of rTMS will be applied during each of the target presentations. The coil will be positioned over the optimal scalp position for activating finger and wrist muscles. Here, 5 pulses at 5 hz will be applied each time that a target appears on the computer screen. In a control task individuals will be asked to perform to follow the same cursor using their lower limb muscles. A total of 1200 rTMS pulses will be applied at80% of AMT intensity (see more details about rTMS application in AIM 2a).

Training+sham rTMS group- Training will be conducted as described above. For sham rTMS, TMS coil will be positioned in the same location as described above. A second coil will be placed behind the subjects head, and it will discharge in the air using the same stimulation parameters that will be used in the TMS application. During sham stimulation only the coil located behind the subjects head will be triggered. Participants may feel small pressure from the coil positioned on top of their head and hear the click sound during triggering.

Measurements before and after rTMS protocols:

Physiology- We will examine: (a) MEPs, SICI, IHI, and F-wave (See procedures in Aim 1). Precision grip motor performance: We will quantify the following outcomes: (a) Force onset [the time point at which force increases 2SD above force baseline], (b) Force rate (maximum derivative of force (force/s) between force onset and target force), (c) Force area (area between force onset and force decay to zero), and (d) Total force duration (time between force onset and force decay to zero).

Motor function- We will use range of motion (ROM), JTT, Pinch force, Chedoke arm and Hand inventory, and sensory function of the upper and lower extremities using the American Spinal Injury Association (ASIA) sensory scores and Electrical Perceptual Threshold (EPT). These functional and sensory tests are described in in detail in Aim 2a.

Plan for multiple rTMS sessions using Brainsight for MRI co-registration: to ensure that the same area of the motor cortex is stimulated during multiple rTMS sessions we will use the Brainsight co-registration system. We will use an MRI scanner located at the University of Miami Applebaum MRI center or at the Miami VA Medical center. Individuals will be asked to participate in the scan session at their convenience as soon as they are enrolled in Aim 1 of this proposal. Individuals who only participate in Aim 2 of the study will be asked to have the MRI session after they have signed the consent form.

Plan for assessment of long-term effects of rTMS: Physiological and behavioral measurements will be acquired before and after sessions 1,5,and 10.

Phase 3- Follow up

Follow up measurements will be taken after 1, 2, and 3 months after Phase 3 testing to measure any sustained improvements in hand function. This assessment will be competed in a single session. These assessments will be the same as in Phase 1-3 of this research study. Each session will last about 1 hour.

Physiological measurements- We will examine MEPs, SICI, IHI, and F-waves (see procedures in Aim1). Precision Grip motor performance: we will examine Force onset, rate, area and total force duration (see procedures in Aim 2a.) Hand motor function: we will examine JTT, Pinch force, Chedoke Arm and Hand inventory, and sensory function of the hand using the American Spinal Injury Association (ASIA) sensory scores (see procedures in Aim 2a).

Assessment of quality of life and functional independence after SCI- the following measurements will be conducted before and after training sessions in Aim 2B, and at the follow up visits 1,2, and 3 months after training.

(a) Self-care subscale of the spinal cord independence measure- Version III (SCIM; itzkovich et al., 2007)

(b) The Capabilities of upper Extremities (CUE; Marino et al., 1998)

Demographics will be collected in all subjects. This will include variable such as age, gender, race, height, weight, and veteran status. For individuals with SCI, we will also collect level of injury and date of injury.

Target population:

Male and female veterans with spinal cord injury at least 1 year after injury was sustained. We also plan to enroll control subjects who do not have any history of spinal cord injury.

Inclusion/Exclusion Criteria :

Participants who are unimpaired healthy controls:

(1) Male and females between ages 18-85 years

(2) Right handed

(3) Able to complete precision grips with both hands

(4) Able to complete full wrist flexion-extension bilaterally

(5) Able to walk unassisted

(6) Able to complete full ankle flexion-extension bilaterally

Participants who have had a spinal cord injury:

(1) Male and females between ages 18-85 years

(2) Chronic SCI (≥ 6 months of injury)

(3) Spinal Cord injury at or above L5

(4) The ability to produce a visible precision grip force with one hand

(5) Individuals who have the ability to pick up a small object (large paperclip) from a table independently

(6) Able to perform some small wrist flexion and extension (measured by a goniometer)

(7) The ability to perform a small visible contraction with dorsiflexor and hip flexor muscles
(8) No subjects will be excluded based on their race, religion, ethnicity, gender or HIV status.

Exclusion criteria for enrollment For SCI and Healthy Control Subjects (for stimulation):

(1) Uncontrolled medical problems including pulmonary, cardiovascular or orthopedic disease

(2) Any debilitating disease prior to the SCI that caused exercise intolerance

(3) Premorbid, ongoing major depression or psychosis, altered cognitive status

(4) History of head injury or stroke

(5) Metal plate in skull

(6) History of seizures

(7) Receiving drugs acting primarily on the central nervous system, which lower the seizure threshold (see appendix 2)

(8) Pregnant females

(9) Ongoing cord compression or a syrinx in the spinal cord or who suffer from a spinal cord disease such as spinal stenosis, spina bifida, MS, or herniated cervical disk

(10) Individuals with scalp shrapnel, cochlear implants, or aneurysm clips.

Qualified subjects can participate in up to 190 visits for this study. Visit range from 1-3 hours in length.

Start date: 11/2015.

Completion Date: 12/2019

E. Risks

This is a minimal risk proposal.

TMS procedures:

The TMS system stimulates the brain non-invasively. It generates a small magnetic field across the subject. TMS is widely used in clinical research, and the risks of TMS are believed to be very low. However, there is the very slight chance that TMS can cause a seizure. There is no ionizing radiation exposure involved and the studies are non-invasive. All participants will be screened before enrollment to assure that they meet study criteria and that there are no contraindications to TMS.

Subjects will be instructed that they can discontinue the TMS experiment at any time. In the unlikely event of a seizure, a medical physician will be contacted for immediate response. If a headache or mild scalp discomfort occurs, subjects will be directed to use over the counter pain medication at their own discretion. Earplugs will be utilized to minimize any type of hearing damage that might possibly occur due to the sound generated by the TMS equipment. Dr. Perez (PI) and/or an authorized team member will conduct TMS procedures as needed.

Dr. Perez has been working with TMS procedures for the last 13 years and has extensive experience in the use of TMS procedures. Although very unlikely, it is theoretically possible that the participant may have a seizure induced by the TMS. Considering the large number of subjects and patients who have undergone TMS studies since 1998 and the small number of seizures, we can assert that the risk of TMS to induce seizures is certainly very low (see review by Rossi et al., 2009). However, we will inform the participant about this unlikely risk. If a seizure occurs, it will occur during the TMS application itself, not after. When a seizure happens the participant's brain starts acting strangely and participants may feel dizzy and have repetitive rhythmic movements of any part of their body. If this unlikely event happens, we will immediately call an attending physician. On weekends, the subject should call the emergency 24 hour pager 305-243-1000 to get in touch with Dr. Alberto Martinez-Arizala, and let him know that he is a research subject from the Miami VA in Enhancement of Motor Function after Spinal Cord Injury.

In the unlikely event of a seizure, a standard seizure protocol will be followed:

1. Cushion the head and area so subject does not injure themselves.
2. Turn the subject on their side to prevent aspiration
3. Monitor the duration of the seizure
4. If the seizure ends in less than 60 seconds, monitor and contact the primary care MD to rule our predisposing factors.
5. If the seizure lasts more than 60 seconds, activate emergency services.

In the event that a seizure occurs on premises and we are unable to reach the physician, 911 will be called for emergency services.

Risks of Muscle Activity Recording (EMG): Mild discomfort, such as an itching sensation may be felt under the electrodes that register the response in your muscles. There may be some pain or bleeding from the needles used for intramuscular recording. The possibility of this is infrequent (occurring in 1-10%, or 1-10 out of 100 people). We will clean the area with alcohol and use standard, hospital grade electrodes, and sterile needles.

Peripheral Nerve Stimulation intensity will be increased gradually during the evaluations when necessary. Mild discomfort, such as an itching sensation may be felt under the electrode that stimulates your wrist or under the electrodes that register the response in your muscles. The possibility of this is infrequent (occurring in 1-10%, or 1-10 out of 100 people). We will clean the area with alcohol and use standard,

hospital grade electrodes. Another risk of the nerve stimulation used in this research is that you might feel mild pain, if pain fibers could be activated.

MRI scan: Subjects, investigators, and facility staff will be examined by a hand-held screening device for magnetic material before entry and each re-entry to the scan room. Warning signs, including the specific dangers of high magnetic fields, are posted in the necessary location. The standard 3 Tesla Magnet will be used for testing. The MRI exam involves no exposure to x-rays or radioactivity, and is safe. The FDA approved the Siemens 3-T scanner, which time varying magnetic fields (gradient), specific absorption rate and acoustic noise levels. FDA guidelines will be strictly enforced at our 3T scanner.

JTT/CAHA/pinch grip/ASIA: individuals will have resting periods as needed, all procedures will be explained in detail and subjects will be informed that they can stop the experiment at any time

Screening Interview: Identifiable information collected during either the screening interview will be destroyed if the potential subject does not qualify. If the subject does qualify and ultimately enrolls into this research, all information collected will become part of their research record. All security precautions that are reflected in this protocol will apply.

Data Collection and Storage: Research records will be retained in accordance with the Veterans Health Administration (VHA) Records Control Schedule. The Federal Privacy Act protects the confidentiality of medical records. Electronically-stored medical information collected from study participants will be kept on a VA server. Electronic data recorded during experimental sessions will be kept on fully-secured computers (password protected) on a VA server. Unique subject identifiers (i.e., a code accessible only to the PI and AI) will be used to label all electronic data files.

F. Sample Size

Up to 500 participants (250 SCI, and 250 control subjects) will be recruited to participate in this study at the VAMHS and at the University of Miami. Based on our previous protocols testing spinal cord injured subjects and healthy control subjects, we have added a 25% attrition rate to the number of subjects we plan to enroll in the study.

All participants will be between 18 and 85 years of age. We plan to recruit both veterans and non-veterans.

G. Data analysis is consistent with the study objective

Aim 1: Repeated-measures ANOVA and Tukey post hoc test will be used to assess the effect of TASK (rest, precision grip/wrist flexion, and precision grip/wrist extension) and GROUP (SCI, controls) on physiological measurements.

Aim 2a: Repeated measures ANOVA and Tukey post hoc test will be used to determine the effect of TIME (0,10, 30, 60 min after a single rTMS session), STIMULATION (rTMS, sham rTMS over control brain area) on physiological and behavioral measurements.

Aim 2b: repeated measures of ANOVA and Tukey post hoc analysis will be used to determine effects of GROUP (training + rTMS, training + sham rTMS), TIME (sessions number 1,5,10 and follow up 1,2,and 3 months) on physiological outcomes and motor performance.

H. Privacy and Confidentiality:

Every effort will be made to make sure that the information about you obtained from this study will be kept strictly confidential. Private information is collected about participants as part of this study. Screening forms are filled out by the study coordinator or other approved study team member by phone or in person. Please see all specific questions asked to participants listed in our "SCI Subject Screening Questions" and "HV Screening Questions" forms. Screening forms are used during the screening session to collect both identifiable information as well as non-identifiable information. The research staff will take every precaution to protect all identity and the confidentiality of the information collected about each subject. Any electronic or hard/paper copies of the information collected will be stored in a secured location. Any copies that contain information that could be used to identify participants (such as their name, address, date of birth, etc.), will be stored separately from any information that does not contain identifiers. Only those individuals who are authorized to review the information will have access to it. Identifiable electronic information related to participants' involvement will be stored on restricted access password protected servers. In order to protect their confidentiality, data that we record about subjects may be sent to the organizations listed above via a secure website, courier and or facsimile. The data that will be shared with the study sponsor will not include any names or any information that may directly identify participants. All data will be coded with the study number, which may include participants' initials.

Information may also be disclosed to the VA Miami Healthcare System Research and Development Office Staff in order to perform duties related to research administration.

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1.0 * Please provide a list of references (Multi-site protocols: You may reference the page numbers in the original protocol):

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