PROTOCOL TITLE: Targeted Neuroplasticity after Spinal Cord Injury

PRINCIPAL INVESTIGATOR:

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Site(s) where study will be performed:

Version Date	8/5/2021
Investigational Agent(s) (Drugs or Devices)	
IND / IDE / HDE #	
Indicate Special Population(s)	☐ Children ☐ Children who are wards of the state ☐ Adults Unable to Consent ☐ Cognitively Impaired Adults ☐ Neonates of Uncertain Viability ☐ Pregnant Women ☐ Prisoners (or other detained/paroled individuals) ☐ Students/Employees N/A
Sample Size	500
Funding Source	Institutional funds/Northwestern University
Indicate the type of consent to be obtained	☒ Written ☐ Verbal/Waiver of Documentation of Informed Consent ☐ Waiver of HIPAA Authorization ☐ Waiver/Alteration of Consent Process
Site	☐ Lead Site (For A Multiple Site Research Study) ☐ Data Coordinating Center (DCC)
Research Related Radiation Exposure	☐ Yes ☒ No
DSMB / DMC / IDMC	☐ Yes ☒ No

OBJECTIVES:

The purpose of this study is to test a strategy to restore upper and lower-limb motor function in individuals with spinal cord injury (SCI). We have the following two specific aims:

Aim 1. Maximize exercise-mediated recovery of limb muscles by using stimulation induced spinal plasticity. We will study the effect of limb training combined with Spike-Timing Dependent Plasticity (STDP) on motor function recovery. We will test the effect of three groups: (1) stimulation, (2) training +stimulation, and (3) training+sham stimulation. We hypothesize that the ability of training to promote recovery of limb motor function will be enhanced by eliciting STDP in upper and lower-limb. An important strength of this aim is the combination of training and STDP, which aims at enhancing the beneficial effects of motor training by promoting plasticity in the corticospinal pathway (Ellaway et al., 2007; Castel et al., 2009). Training effects on physiological pathways will be explored and correlated with hand/arm motor function and the site and extent of the lesion defined by structural MRI.

Aim 2. Maximize exercise-mediated recovery of limb muscles by using stimulation induced spinal plasticity. STDP has been shown to be effective in enhancing the recovery of residual limb function in humans with chronic incomplete SCI (Urbin et at., 2017). In this aim we will investigate the effect of the combination of extended STDP and training. We hypothesize the ability of training to promote recovery of motor function will be enhanced by eliciting STDP in the corticospinal pathway.

BACKGROUND:

After a SCI, many individuals present deficits in upper-limb and/or lower-limb function. Most SCIs are contusions and ~50% occur at the cervical level causing anatomically incomplete damage and bilaterally functional deficits to lower- and upper-limbs (Kakulas, 1999). Arm and leg function deficits limit daily-life activities, such as reaching and grasping, eating, writing, and walking which decreases the quality of life (Snoek et al., 2004). Regaining arm and leg function is considered the highest priority for improving the quality of life of individuals with SCI (Anderson, 2004).

Rehabilitation strategies in humans with SCI rely on the use of exercise (Harkema et al., 2012; Behrman et al., 2017). Exercise training aims to drive neural networks in an activity-dependent manner to elicit plasticity and facilitate functionally relevant muscle activity below the level of injury (Knikou, 2010). Studies using animals (Courtine et al., 2009; Hill et al., 2009; McPherson et al., 2015) and humans (Rejc et al., 2017; Gad et al., 2018; Gill et al., 2018) agree that physiological and functional effects of exercise can be augmented by the use of neural stimulation, which is thought to increase the likelihood of activating spared neural pathways. Even though these approaches have facilitated exercise-mediated recovery, the overall effects remain limited. Clearly, there is a need to develop interventions that can more effectively engage spared neural connections to further improve functional recovery due to rehabilitative exercise in humans with SCI.

Evidence has shown that corticospinal transmission can be enhanced by precisely timing pairs of presynaptic and postsynaptic action potentials arriving at the spinal cord (Taylor & Martin, 2009),

which can enhance voluntary motor output in humans with (Bunday and Perez, 2012) and without (Taylor & Martin 2009) SCI. Evidence has shown that the activity in upper-limb muscles can be enhanced by activations of the lower limb (Zhou et al., 2017). Therefore a strategy that combine upper and lower limb stimulation and activity might be more effective to enhance upper limb function. In this protocol, we will test the effect of training combined with stimulation to facilitate upper and lower limb function.

How STDP and training might contribute to recovery of upper-limb and lower-limb function: The physiological basis for these protocols comes from animal studies showing that an increase or decrease in synaptic strength can be elicited by repeated pairs of presynaptic and postsynaptic action potentials that are precisely timed with respect to each other (Bi & Poo, 1998; Dan & Poo, 1998; Bi & Poo, 2001). If antidromic stimulation of a postsynaptic cell is paired with timed orthodromic stimulation of a presynaptic cell, bidirectional plasticity can be induced (Bi & Poo, 1998; Markram et al., 1997). In humans, corticospinal neurons can be activated by transcranial magnetic stimulation (TMS), and antidromic action potentials can be elicited in sensorimotor cortex and motoneurons by peripheral nerve/ spinal cord stimulation. STDP has been used successfully to precisely pair pulses to arrive at the spinal cord (Taylor & Martin, 2009). How to strengthen synaptic plasticity in corticospinal connections targeting the spinal cord (spinal synapses) of upper-limb and lower-limb muscles after SCI combined with training and its effect on voluntary output, remains unknown and will be investigated in this study.

STUDY ENDPOINTS:

The primary outcome measure utilized in this part of study is the Graded Redefined Assessment of Strength, Sensibility and Prehension (GRASSP see below). GRASSP is an extensive and validated impairment and functional measure which is able to detect subtle neurologic changes in individuals with spinal cord injury. Specifically, it evaluates the domains of sensation, strength, quality of different grip patterns and the ability to complete a variety of functional tasks.

The primary outcome measure utilized in this part of study the 10-meter Walk test. In the group receiving lower-limb exercises, we will use the 10-meter walk test to assess walking speed in meters per second. The same percentage of body-weight support will be used during pre- and post-assessments. A stopwatch will be used to measure the time to execute the task. The 10-meter walk will be repeated 3 times and the average will be used.

Participants may complete the following secondary endpoint measurements before and after the STDP protocol as outlined below.

A). MEPs: Transcranial magnetic stimuli (TMS) will be delivered from a Magstim 200 stimulator (Magstim Company) through either a figure-of-eight coil (loop diameter, 7 cm) or a double-cone coil (used for the tibialis anterior muscle) with a monophasic current waveform. TMS will be delivered to

the optimal scalp position for activation of dominant muscles in controls and the furthest muscle with residual connectivity below the level of injury in individuals with SCI. The optimal scalp position will be determined by moving the coil in small steps along the hand/arm/leg representation of the primary motor cortex to find the region where the largest MEP can be evoked with the minimum intensity in the targeted muscle(s). The muscles to be activated will be the first dorsal interosseous, abductor pollicis brevis, flexor and extensor carpis radialis, biceps and triceps brachii, deltoid, quadriceps femoris, hamstrings, tibialis anterior and soleus. Measurements: resting (minimum intensity required to induce MEPs greater than 50 μV in 5/10 consecutive trials at rest), and active (minimum intensity able to evoke an MEP bigger than 200 μV in 5/10 consecutive trials during 5-10% of MVC) motor threshold. Thirty MEPs will be average in each condition.

B). CMEPs: Supramaximal electrical stimulation will be administered posterior to the mastoid process or thoracic spine to elicit motor evoked potentials to upper- and lower-limb muscles.

C). Motoneuronal excitability (reflected by F-wave persistence and amplitude): Using supramaximum stimulus intensity (120% of the maximal motor response, M-max; 0.2 ms duration, 20 trials (88)) to the ulnar nerve at the wrist for the first dorsal interosseous, median nerve at the wrist for abductor pollicis brevis, brachial plexus at the erb's point for the deltoid and biceps brachii, femoral nerve for quadriceps, and common peroneal nerve under the head of the fibula for the tibialis anterior and posterior tibial nerve behind the knee joint for the soleus. We will quantify latency, peak-to-peak amplitude of each F-wave, and F-wave persistence (number of F-waves present on each set).

D) H-reflex: Quadriceps femoris H-reflex and M-max: Participants are comfortably seated in an armchair. Percutaneous electrical stimulation of the femoral nerve will be delivered (using 1 ms rectangular electrical stimulus, DS7AH, Digitimer Ltd.) through a cathode (10-mm diameter Ag-AgCl electrode) placed in the femoral triangle and an anode (Ag-AgCl plaque) placed over the posterior aspect of the thigh. Stimulus intensities will be increased in steps of 0.05 mA, starting below H-reflex threshold and increasing up to measure the H-max and M-max at rest (0.25 Hz). The H-max and Mmax will be measured as peak-to-peak amplitude of the non-rectified response in control subjects and both legs of individuals with and without spasticity as determined by the MAS. MAS this clinical scale will be used by measuring resistance encountered during manual passive muscle stretching using a six-point ordinal scale (0=no increase in tone, 1/+1=slight increase in tone with a catch and release or minimal resistance at the end or less than half of the range of movement, respectively, 2=more marked increased tone through most of the range of movement but affected parts easily moved, 3=considerable increase in tone and passive movement difficultly, and 4=affected parts rigid; Bohannon and Smith, 1987). Tibialis anterior H-reflex and M-max: Participants will be comfortably seated in an armchair. Percutaneous electrical stimulation of the common peroneal nerve will be delivered (using 1 ms rectangular electrical stimulus, DS7AH, Digitimer Ltd.). Stimulus intensities will be increased in steps of 0.05 mA, starting below H-reflex threshold and increasing up to measure the H-max and M-max at rest (0.25 Hz). The H-max and M-max will be measured as peak-to-peak

amplitude of the non-rectified response in control subjects and both legs of individuals with and without spasticity as determined by the MAS. Soleus H-reflex and M-max: Participants will be comfortably seated in an armchair. Percutaneous electrical stimulation of the posterior tibial nerve will be delivered (using 1 ms rectangular electrical stimulus, DS7AH, Digitimer) through a cathode (10mm diameter Ag-AgCl electrode) placed in the popliteal fossa over the posterior tibial nerve and an anode (Ag-AgCl plaque) placed over superior to the patella. Stimulus intensities will be increased in steps of 0.05 mA, starting below H-reflex threshold and increasing up to measure the H-max and Mmax at rest (0.25 Hz). The H-max and M-max will be measured as peak-to-peak amplitude of the non-rectified response in control subjects and both legs of individuals with and without spasticity as determined by the MAS.

E) EMG and force voluntary output: Individuals will perform a maximum voluntary contraction (MVC) of the targeted muscles (deltoid, biceps brachii, first dorsal interosseous, abductor pollicis brevis, quadriceps femoris, tibialis anterior and/or soleus) through surface electrodes secured to the skin over the belly of each muscle (Ag-AgCl, 10 mm diameter). The signals will be amplified, filtered (20–1000 Hz), and sampled at 10 kHz for offline analysis.

F) Nine Hole Peg Test (9HPT): This test measures finger dexterity. The board is placed at the participant's midline, with the container holding the pegs facing toward the hand being tested. Nine small pegs are placed in a container and subjects are instructed to pick up each of the pegs and put them back as fast and accurately as possible. The time to complete the task is measured in seconds.

G). Jebsen Taylor Test (JTT): This test measures hand function. The time in seconds to complete subcomponents of the JTT will be measured for both hands.

H) Chedoke Arm and Hand inventory (CAHAI): This test measures upper-limb motor recovery. Quantitative scale with 13 items (each item is given a score: 1 to 7).

I) Electrical Perceptual Threshold (EPT): This test provides a quantitative measure of sensory function by using small pulses of electricity on the surface of the skin and will be used to evaluate sensory threshold in the hands/arms and legs.

J) Kinematics: These will be measured during self-paced and fast grasping or walking movements recorded by OptiTrack V100 cameras (120 Hz) and by Opti Track, V120: Trio camera, NaturalPoint, Inc., with cameras respectively for the locomotor training. Subjects will be seated and grasp with the less affected (participants) and dominant (controls) arm. Cameras will be positioned in front/sides of subjects with markers on the tip of the thumb and index finger, inner side of the wrist, lateral size of the elbow and shoulder joints. Variables: 1) Movement onset (MO): time between the GO signal and start of forward arm velocity. 2) Total movement duration (MD): time between MO and grasp (Gr=time when index and thumb contact target). MD will be broken in

time to reach maximum velocity (MV), maximum hand aperture (MA), and the first finger contact (FC), and Gr.

K) Startle: We will test the StartReact response to assess contributions from the reticulospinal tract. Participants will be asked to observe a red LED located ~1 m in front of them. When the LED is illuminated, individuals will be asked to perform as fast as possible isometric muscle contractions. In some trials, the LED will be presented with a quiet (<95 dB; 50 ms) or a startling (SAS, >115 dB; 50 ms) acoustic stimulus. We will measure: (a) visual reaction time (defined as the onset of the EMG burst in the contracted muscle after the LED), (b) auditory reaction time (time delay between the presentation of the quiet acoustic stimulus and the onset of the EMG response), and (c) visual+startle reaction time (time between the SAS and the EMG onset).

L) Pendulum Test: As part of the physical exam, we will use the pendulum test to measure muscle tone at the knee by using gravity to provoke muscle stretch reflexes during passive swinging of the lower limb.

M) Portable Spasticity Assessment Device (PSAD): The PSAD combine biomechanical and electrophysiological measurements for an objective quantification of active and passive component of muscle stiffness (Lorentzen et al., 2017). The device functions as a dynamometer integrating measurement of force, joint movement, and reflex-mediated muscle activity.

N) Toronto Rehabilitation Institute-Hand Function Test (TRI-HFT): This exam measures gross motor function frequently used to manipulate objects that participants may encounter in their daily lives. The first part of the test evaluates manual hand dexterity through the ability to use lateral/pulp pinch and palmar grasp to manipulate common objects in three different gravity-related positions: against gravity (supination), toward gravity (pronation), and in a gravity-eliminated plane (mid-prone position). To test the palmar grasp, participants are presented with a: mug, book, soda can, isosceles triangular sponge, and wireless telephone. To test lateral pinch and precision grip, participants are presented with a: paper sheet, Ziploc bag filled with five golf balls, dice, credit card, and pencil. The second part of the test measures the strength of their lateral/pulp pinch and palmar grasp. Participants are presented with nine rectangular blocks, instrumented cylinder, credit card attached to a dynamometer and wooden bar used to measure the torque generated by palmar grasp, the force that the pinch (lateral or pulp) grasp could resist, and the eccentric load that the palmar grasp could sustain. There is no time limit within which the task must be performed. The scoring system is designed to emphasize the type of grasp used to accomplish the task: an active (i.e. ability to develop active finger) or passive (i.e. positioning of the proximal joints) grasp (Kapadia et al., 2012).

O) Neuromechanical hand testing: This exam will measure stretch reflexes flexor and extensor carpi radialis and first dorsal interosseous using a previously described method (Kamper et al., 2001). Stretch reflexes will be elicited by rotation of the wrist joint for flexor and extensor carpi

radialis, and by rotation of the metacarpophalangeal joint for first dorsal interosseous. The arm will be positioned along the trunk, with the elbow flexed at 90° and secured to the device. The wrist and metacarpophalangeal joint will be aligned with the forearm in a neutral position and secured to the motor shaft through a jig such that rotation of the shaft produced rotation of the targeted joint. Rotation will be performed from the maximal joint flexion/extension position. Ten trials will be performed with a few minutes between trials to minimize effects of repeated stretching on subsequent responses.

P) Stretch reflexes: We will use a Kinesiological Instrument for Normal and Altered Reaching Movements (KINARM) to examine elbow stretch reflexes change related to spasticity. The KINARM is capable of applying loads at elbow joints using torque motors while angular position and angular velocity are recorded. Briefly, participants will sit with their arms resting in troughs with shoulders abducted ~85°. Shoulder and elbow joints will be aligned with the linkages of the robot and movement will be permitted in the horizontal plane. Physical stops do not allow the elbow to hyperextend. Elbow angle, fingertip position, and segment length for both arms will be calibrated for each participant. The kinematic assessment of spasticity consists of elbow joint stretches by moving the forearm from maximal elbow extension to maximal elbow flexion and in the opposite direction to assess passive and active muscle stiffness, respectively. EMG activity will be recorded from biceps and triceps brachii of the right arm through bipolar surface electrodes (Ag-AgCl, 10-mm diameter, 1 cm apart) secured on the skin. Ten trials will be performed with a few minutes between trials to minimize effects of repeated stretching on subsequent responses. Elbow angular position and velocity will be sampled at 1000 Hz using Dexterit-E (BKIN Technologies Ltd., Kingston, Canada) and analyze with MATLAB (MathWorks, Natick, MA). Range-of-motion, torque, and stretch reflex will be analyzed as well as first angle (i.e., the angle at an angle (i.e., angle at the final position following the release after the “catch”).

Q) Modified Ashworth Scale (MAS): This scale measures resistance encountered during manual passive muscle stretching using a six-point ordinal scale. During testing of elbow flexor and extensor muscle, subjects will sit comfortably in a chair with their arm in a supine position. The elbow joint will be stretched by moving the forearm from maximal elbow extension to maximal elbow flexion (triceps brachii spasticity assessment) and in the opposite direction (biceps brachii spasticity assessment). The knee extension and ankle extension and flexion will performed to assess spasticity in quadriceps and tibialis anterior and soleus respectively. The same rater will perform all MAS assessments.

R) Participant reported spasticity: Individuals with SCI will grade the severity of spasticity with a four-point nominal scale (0=none; 1=mild; 2=moderate; 3=severe) to answer questions: 1) how would you rate the severity of your spasticity in your right biceps brachii, 2) triceps brachii, 3) quadriceps, and 4) tibialis anterior, 5) soleus?

S) Surveys: All SCI participants will be asked to complete the following SCI-CAT surveys during the pre-assessment and at the post-40 visits:

(a) Ambulation: This questionnaire will ask the participant about their ability to do thing like walk, run and jump.
(b) Basic Mobility: This questionnaire will ask the participant about their ability to perform their daily routine.
(c) Fine Motor: This questionnaire will ask the participant about their ability to pick up small objects.
(d) Manual and Power Wheelchair Mobility: This questionnaire ask the participant about their ability using a wheelchair.
(e) Self-Care: This questionnaire will ask the participant about their ability to do activities of daily living such as getting dressed, bathing, and eating.

STUDY INTERVENTION(S) / INVESTIGATIONAL AGENT(S):

STDP protocol:

STDP and sham-STDP: During STDP, participants will have a maximum of 360 paired pulses of stimuli delivered every 1-10 s (~60 min) and a small cohort of participants (n=10) will have a maximum of 720 paired pulses of stimuli (up to 4 times per day) using the same delivery period. Corticospinal volleys will be evoked by TMS over the primary motor cortex and/or the spinal cord will be timed to arrive at corticospinal-motoneuronal synapses of each muscle ~1-2 ms before antidromic potentials evoked in motoneurons by peripheral nerve stimulation (PNS) and/or spinal root stimulation. During sham-STDP, a coil will be placed on the scalp of the participant to provide the participant with the feeling of having the coil on their head. This coil will not be connected to a TMS or any other device. A second coil will be placed ~10 cm behind the subject's head and triggered in the air every 1-10s for up to 720 stimuli to provide the subject with the same auditory sound produced by the TMS as the non-sham.

TMS: Transcranial magnetic stimuli will be delivered from a Magstim 200 stimulator through either a figure-of-eight coil or a double-cone coil (used for the tibialis anterior muscle) with a monophasic current waveform. TMS will be delivered to the optimal scalp position for activation of the targeted muscle. The optimal scalp position will be determined by moving the coil in small steps along the hand/arm/leg representation of the primary motor cortex to find the region where the largest MEP can be evoked with the minimum intensity in the targeted muscle. This scalp position will be saved using a stereotaxic neuro-navigation system (Brainsight 2). 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 stimuli will be delivered at an intensity from motor threshold to 100% of the maximum stimulator output.

PNS/Spinal root Stimulation: Supra-maximum electrical stimulation (200 μs pulse duration, using Digitimer DS7AH or DS7R, Cosyma BioStim-5) will be delivered to the ulnar nerve at the wrist for the first dorsal interosseous, median nerve at the wrist for abductor pollicis brevis, brachial plexus at the erb's point for the deltoid and biceps brachii, common peroneal nerve under the head of the fibula for the tibialis anterior, posterior tibial nerve for soleus, and/or spinal cord segments in the thoracic/lumbar spine. The anode and cathode will be placed approximately 3 cm apart and 1 cm in

diameter with the cathode positioned proximally. The stimuli will be delivered at an intensity of 120% of the M-max for each muscle.

TMS and PNS/spinal root interstimulus interval (ISI). The ISI between TMS and PNS/spinal root stimulation will be set to allow descending volleys elicited by TMS to arrive at the presynaptic terminal of corticospinal neurons ~1-2 ms before antidromic PNS/spinal root volleys reach the motoneurons reach during STDP. The methods for timing the arrival of volleys at the spinal cord have been described previously (Bunday and Perez, 2012; Urbin et al., 2017; Bunday et al., 2018). Briefly, the ISI will be tailored to individual subjects based on conduction times calculated from latencies of MEPs, F-wave, and M-max. MEP latencies will be recorded during isometric ~10% of MVC of the target muscle to determine the shortest and clearest response for our estimations. The onset latency will be defined as the time when each response exceeds 2 SD of the mean rectified pre-stimulus activity (100 ms) in the averaged waveform. Peripheral conduction time (PCT) will be calculated using the following equation:

$$PCT = (\text{F-wave latency} - \text{M-max latency}) \times 0.5$$

Central conduction time (CTT) will be calculated using the following equation:

$$CCT = \text{MEP latency} - (PCT + \text{M-max latency})$$

Upper limb training

All participants will exercise immediately after the stimulation paradigm. Upper-limb exercises will involve gross grasping, fine grasping, and hand cycle using an arm ergometer. During gross grasping, subjects will be asked to reach and grasp cylinders, blocks, cups and lids randomly presented on a table located in front of them at a height of ~20 cm. Then, subjects will be asked to reach and grasp the object to put it back on the table. These sets of movements will be repeated 20 times for each object with breaks as needed. During fine grasping, participants will perform similar movements but they will be asked to reach and grasp smaller objects (peg, bead, pinch pin, cube). During hand cycle, the arm ergometer will be used for 15 minutes and grasping gloves will be used as needed. Movements will be passive, active-assisted, or active depending on participant's ability to perform tasks. In addition, training will consist of grasping with the thumb and index finger targets of different diameters (1, 2.5, and 6 cm) in a vertical board (36x30") positioned in front of them. The board will contain 6 panels (12x15") which will light up individually by a computer cue. Each panel will have three LED lights to indicate grip strength to be exerted (red=30% MVC, blue=20% MVC, yellow=5% MVC). A reflective line in each target will identify the place to grasp, which will be modified to increase task difficulty. Force transducers will run along the sides of each target to communicate with LEDs. Kinematics and EMG signals will be acquired through surface electrodes. Subjects will be instructed to grasp the object between index finger and thumb as fast and accurately as possible holding the final posture for 3 s until the light disappear. 300 trials will be completed.

Lower Limb Training

All participants exercised immediately after STDP or sham-STDP. Lower-limb exercises will involve over-ground walking, treadmill walking, and stair climbing training. During locomotor training, subjects will use a body-weight support system with ~0-70% of body weight support. During treadmill training, subjects will walk at a speed of 0.1-0.3 m/s for 10 minutes using the body-weight support system. During stair climbing, subjects will climb up and down 4 steps with 3 full repetitions. Locomotor training+STDP protocol: In each session, STDP stimulation will be targeting the leg muscles at rest, and their effects will be tested on voluntary contractions. Locomotor training will be preceded by the STDP protocol. The locomotor training will consist of walking. The amount of weight support will be provided as needed by a body-weight support system and the level of support will be associated with gait kinematics which resemble unsupported walking. The body-weight support system is a robotic over ground arrangement for practicing a wide range of activities without the risk of falling. The support will be adjusted within and between sessions as necessary to prevent excessive knee flexion during stance phase or toe dragging during swing phase (Finch et al., 1991). Subjects will be encouraged to walk at their comfortable speed at which step kinematics are acceptable (no toe dragging, an adequate knee flexion during swing phase, adequate knee extension at initial stance phase, etc.). All subjects will be allowed to rest as needed during the training sessions. The starting and end points and guiding path will be marked with lines on the floor. Thirty five retro-reflective markers will be attached to the participant's body according to the Plug-In-Gait market set. While the participant is walking on the path, joint movements will be acquired by a 3dimensional motion capture system. The locomotor training session will consist of at least 3 sessions are expected to be completed per week as the participant is able. Missed sessions will be rescheduled according to the subject's availability.

STUDY TIMELINE:

Participants will be initially screened over the phone or in person to ensure eligibility based on established inclusion and exclusion criteria.

If eligible, participants will be asked to complete pre, post, and follow-up assessment sessions in addition to the training sessions. Each assessment will require 2-5 sessions. Participants will complete up to 135 training sessions with a maximum of 360 paired pulses of stimulation and a small cohort of participants (n=10) will complete up to 270 training sessions with a maximum of 720 paired pulse of stimulation (up to 4 times per day). This will be determined based on preliminary data. In Aim 1, participants will be tested before and after at least 10 training sessions with single site stimulation. In Aim 2, participants will be tested before and after at least 40 training sessions with multisite stimulation. If a training session is not completed or missed participants will be asked to recover that session in a timely manner.

AIM 1: Randomized controlled design

Pre-assessment:	Stimulation	Post-assessment:	Follow-up assessment:
1. Physiology 2. Kinematics 3. Function	Training + stimulation Training + sham stimulation	1. Physiology 2. Kinematics 3. Function	1. Physiology 2. Kinematics 3. Function

AIM 2:

Pre-assessment:		Post-assessment:	Follow-up assessment:
1. Physiology 2. Kinematics 3. Function	Training + stimulation	1. Physiology 2. Kinematics 3. Function	1. Physiology 2. Kinematics 3. Function

We anticipate that each participant will take about 2-10 months to complete the study procedures/testing. Follow-up assessments will be done 1-9 months after completion of protocol, one follow-up in the first 3 months and the last follow-up in the 4-9 months following the last completed session. We will evaluate the subject's ability to move their hands, arms, legs, feet and/or toes using the different physiological and functional tests as mentioned above. TMS measurements, CMEPS and EMG recordings may also be done at these follow-up assessments.

INCLUSION AND EXCLUSION CRITERIA:

We anticipate the screening of 500 subjects across the two aims (60 subjects for Aim 1, and 40 for Aim 2) who have incomplete SCI at the cervical/thoracic/lumbar level (C2-L2). This number accounts for an attrition rate of 50%. To account for screen failures we would like to ask for a total of 200 subjects.

- Inclusion criteria for SCI subjects:
  - (1) Male and females between ages 18-85 years
  - (2) SCI at least 4 weeks post injury
  - (3) Spinal Cord injury at or above L2
  - (4) ASIA A,B,C, or D, complete or incomplete
  - (5) Possess the following abilities
    (Aim 1) The ability to produce a visible precision grip force with one hand, and/or the ability to perform some small wrist flexion and extension (Aim 2) The ability to perform a small visible contraction with dorsiflexion and hip flexor muscles

- Exclusion criteria for SCI Subjects:

  (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) Vascular, traumatic, tumoral, infectious, or metabolic lesion of the brain, even without history of seizure, and without anticonvulsant medication

  (6) History of seizures or epilepsy

  (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 disk

  (10) Metal plate in skull

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

RECRUITMENT METHODS:

We anticipate screening of 500 subjects to complete the study (see description above). We will be using the IRB approved SCI registry for recruitment. A letter granting access to the registry is included in the submission. Subjects who have previously expressed an interest in participating in research studies at the Shirley Ryan AbilityLab complete a questionnaire and request that their information be entered into the research volunteer database. This database is searchable based on criteria such as age, time-post injury and injury level. Potential subjects will be called by the study coordinator. If the individuals have not agreed to be contacted by phone for future studies then the treating physician will be the one contacting them. The phone call will be to provide information about the study to the individual to determine if they are interested in the study. We will not be collecting any information from the individual. All the screening will be done after written consent is collected and before enrollment.

COMPENSATION FOR PARTICIPATION IN RESEARCH ACTIVITIES:

Participants will be paid $30 for each testing/assessment session (anticipated to last up ~2-3 hours). Participants will be compensated an additional $10/hour for each additional hour, if it is surpassed. There is not compensation for each of the stimulation+training sessions. The funds will be issued to your ClinCard when the visit is complete. The funds will be available within 1 day after being loaded and can be used at your discretion.

Due to the ongoing circumstances of COVID-19, we would like to avoid having the subjects travel to and from the hospital with public transportation. In the event that public transportation is the subjects only transportation, we will ask the subject to take a Taxi/Uber/Lyft and the cost of the Taxi/Uber/Lyft will be reimbursed if a receipt is provided.

Upon enrollment in the study participants will be issued a ClinCard, which is a specially designed debit card for clinical research. When a visit is completed, funds will be approved and loaded onto the card. The funds will be available within 1 day after being loaded and can be used at the participant's discretion. Participants be issued one card for the duration of their participation. If the participant already possess a ClinCard, no new card will be issued and the funds will be loaded as appropriate. If the card is lost or stolen, please call (866) 952-3795 or ask a coordinator for a replacement ClinCard.

Fees are incurred if used at an ATM (fees vary by location). However, if the card is used for in-store or online purchases via credit or debit, or presented to a bank teller, there are no associated fees and no expiration date.

Please be advised: Inactivity on the card for more than 3 months will incur a monthly fee. However, as long as there is activity on the card within 3 months (funds are added or a transaction is completed), the month period will reset and no monthly fee will be assessed. If the participant do incur a monthly fee, please contact Greenphire Support at the number on the back of the card and they will reverse the fee. See "Tips for Using the Attached ClinCard" for more information. The Finance Department at the Rehabilitation Institute of Chicago will be provided with the participant's information, including their Social Security Number, in order to issue payment for the study participation. Study payments are considered taxable income and reportable to the Internal Revenue Service (IRS). An IRS Form 1099 will be sent to the participant if the total payments are $600 or more in a calendar year.

The participant may be given access to new inventions that are being developed by the investigator, the study sponsor, or other people involved in the study. Certain laws can make it harder to obtain legal protection for a new invention shared with a study participant, unless the study participant agrees to keep information about the invention confidential. The participant agree to keep confidential information they may receive about new inventions, such as new drugs, new devices, or new methods.

WITHDRAWAL OF PARTICIPANTS:

Subjects will be allowed to withdraw from the study at any time upon request. Their participation will be terminated if any of the inclusion criteria ceases to be valid or if any exclusion criteria will manifest after enrollment. Occurrence or participant reporting of any of the following during the course of the study may lead to withdrawal by study team:

- Change in dosage for neuro-active medications (Baclofen, Lyrica, Celebrex, Cymbalta, Gabapentin, Naprosyn, Diclofenac, Diazepam, Tramadol, etc.) within 2 weeks of any study visit.
- Skull fractures, skull deficits or concussion within the last 6 months
- Unexplained recurring headaches
- Sleep deprivation, alcoholism
- Claustrophobia precluding MRI
- Pregnancy

RISKS TO PARTICIPANTS:

Muscle Activity Recording (EMG): Mild discomfort, such as tingling, an itching sensation may be felt under the electrodes that register the response in the participants muscles. We will clean the area with alcohol and use standard, hospital grade electrodes.

Peripheral Nerve Stimulation/Spinal stimulation/MEPs/CMEPs/H-Reflex: Intensity will be increased gradually during the electrical stimulation evaluations when necessary. Mild discomfort, such as an itching sensation may be felt under the electrode that stimulates the targeted nerve(s) or under the electrodes that register the response in the muscle(s). 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 participants might feel mild pain, if pain fibers could be activated. Skin irritation due to the use of self-adhesive surface electrodes is possible but will be minimized by cleaning the skin with alcohol before and after the application of the electrodes.

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. Subject Screening. The magnetic field will affect any metallic object. In order to avoid risks associated to heating or motion of metallic parts in the body, all individuals will be carefully screened and will have to complete a safety check form (separate file uploaded in the documents list). Potential Risks. Some individuals feel uncomfortable in enclosed spaces, as in the MRI (claustrophobia). The individual can stop the test at any time by squeezing an emergency stop squeeze ball he/she will hold in their unimpaired hand.

JTT/9HPT/CAHAI/GRASSP/EPT/TRI-HFT: 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.

Portable Spasticity Assessment Device (PSAD): Mild discomfort, such as tingling, an itching sensation may be felt under the electrodes that register the response in the participants muscles. We

will clean the area with alcohol and use standard, hospital grade electrodes. Possible skin irritation from the attachment of arms straps.

Neuromechanical Testing: There is the potential to cause too much stretching, which may cause pain or damage to the joint. A number of safety features are implemented to attempt to reduce these risks, such as mechanical stops and limit switches. Research staff will monitor the subject while using this equipment.

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, ROC stat will be contacted immediately. 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 available to minimize any type of hearing damage that might possibly occur due to the sound generated by the TMS equipment. An authorized study team member will be present during all 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 individuals 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 ROC stat.

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 ROC stat.
5. If the seizure lasts more than 60 seconds, activate emergency ROC stat services.

Spinal stability for inpatient subjects with cervical injuries: TMS over the primary motor cortex and cervical roots and also electrical stimulation applied over the brachial plexus and the spinal cord can general neck muscle contractions and head movement. Therefore, testing will be conducted using head and neck support. We will use the patient's own cervical-collar/neck brace during

testing. In the event a patient is not using a cervical collar/neck brace, we will provide a neck brace for use during testing. In addition, to ensure that there are no concerns about spine stability, prior to enrolling a patient with any injury level, we will get a written authorization from the patient's neurosurgeon and/or SCI care physician at the SRALab approving the patients' participation in all study procedures.

Subjects Screening: Individuals with brain and spinal cord injury are commonly recruited for noninvasive brain stimulation studies, and providing they have no history of seizure disorder and do not meet any of the other exclusion criteria as determined by the TMS safety check (separate file uploaded in the documents list), they are a clinical population to which TMS can be safely applied. All individuals will be carefully screened for the following contraindications to TMS (as listed in the protocol, consent form, and separate TMS safety checklist): pacemakers, metal implants in the head region, history of epilepsy or seizures, skull fractures or skull deficits, concussion within the last 6 months, unexplained recurring headaches, medications that lower seizure threshold, and pregnancy), changes in neuro-active medication dosing within 2 weeks of baseline assessments and across the duration of the study. Individuals with any such contraindications will be excluded from the study. Therefore those individuals included will only be those to which TMS can be safely applied. A majority of the studies conducted by our collaborators over the last 10 years have included patients with brain and/or spinal cord injury, and no reportable adverse events have occurred during TMS interventions similar to this proposal.

Statistical Analysis:
Aim 1: Repeated-measures ANOVA and Tukey post hoc analysis will determine effects of GROUP (stimulation, training+stimulation, and training+sham), TIME (before, immediately after, and follow-ups around 3 and 6 months post intervention) on physiological and behavioral outcomes. For alpha (type I error) of 0.05 and 1-beta (power) of 0.8, 45 SCI participants (15/group) will be included.

Aim 2: Repeated-measures ANOVA and Tukey post hoc analysis will determine effects training stimulation, TIME (before, immediately after, and follow-ups around 9 months post intervention) on physiological and behavioral outcomes. For alpha (type I error) of 0.05 and 1-beta (power) of 0.8, 11 SCI participants will be included.

Audio/Video Taping:

We plan to audio and video taping some parts of the experimental session, upon subject consent (optional in the consent form). Recordings will be only of the experimental activities described in the protocol. The subjects' identity will be hidden if subjects do not explicit consent to be recognized from the video or audio. The audio and video records will be stored in a password-protected file on a USB drive in a locked cabinet in the PI's office at the Rehabilitation Institute of Chicago.

The audio and video records will be used only for:

a) Medical or scientific publications;
b) Presentation at conferences;

The audio and video records will be destroyed after the time period chosen in the consent form.

This study does not involve any other risk to the subject, beyond some sense of effort and mild fatigue. Fatigue will be assessed based on the subjects' verbal report. They will be explicitly invited to interrupt the experiment if they experience fatigue. All studies will be carried out in the hospital environment were medical care is immediately available if needed.

POTENTIAL BENEFITS TO PARTICIPANTS:

Participation in the experiment may result in no direct improvement or, in the rare and unanticipated event, worsening of the subject's condition, including prolonged recovery time.

DATA MANAGEMENT AND CONFIDENTIALITY:

Every effort will be made to make sure that the information about the participant obtained from this study will be kept strictly confidential. Private information is collected about participants during the screening sessions as part of this study. Once the necessary information is collected it is placed into a secure cabinet in a locked room. 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.

PROVISIONS TO PROTECT THE PRIVACY INTERESTS OF PARTICIPANTS:

Interviews and research procedures will be conducted by approved members of the research team in private areas within the Shirley Ryan Abilitylab. Information to be collected will be limited to the amount necessary and specified in this submission to complete research specific aims and study goals.

COMPENSATION FOR RESEARCH-RELATED INJURY:

No compensation is available in the event of research related injury.

ECONOMIC BURDEN TO PARTICIPANTS:

Taking part in this research study will not lead to any costs to the participant.

CONSENT PROCESS:

Subjects will be given or sent a copy of the Informed Consent form to be read before the consenting procedure begins. When the subject (and his/her family/friends) have had a chance to read the consent form a meeting will be scheduled to review the consent form, discuss study procedures in detail, and answer any questions the subject may have. The consent process will be done with either Principal Investigator or another member of the approved study team.

NON-ENGLISH SPEAKING PARTICIPANTS:

Non-English speaking participants are excluded from our study population as we will not be utilizing a translator.

PROTECTED HEALTH INFORMATION (PHI AND HIPAA):

Participants will first complete written informed consent and complete appropriate HIPPA forms prior to participation. A HIPPA form will be obtained from all participants. We are committed to respect the participant's privacy and to keep their personal information confidential. When choosing to take part in this study, the participant is giving us the permission to use their personal health information that includes health information in their medical records and information that can identify them. For example, personal health information may include their name, address, phone number or social security number. The participant's health information we may collect and use for this research includes:

- Medical history
- Results of physical examinations
- Questionnaires
- Records about study devices
- Billing information

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Appendix 2
Medications that may lower seizure threshold

Intake of one or a combination of the following drugs forms a strong potential hazard for application of TMS due to their significant seizure threshold lowering potential: imipramine, amitriptyline, doxepine, nortriptyline, maprotiline, chlorpromazine, clozapine, foscarnet, ganciclovir, ritonavir, amphetamines, cocaine, (MDMA, ecstasy), phencyclidine (PCP, angel's dust), ketamine, gamma-hydroxybutyrate (GHB), alcohol, theophylline.