

University at Buffalo Institutional Review Board (UBIRB)

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Complete Research Protocol (HRP-503)

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Template Instructions

Sections that do not apply:

- *In several sections, the addition of checkboxes for **Not Applicable** have been added to the template as responses.*
 - *If an N/A checkbox is present, select the appropriate justification from the list.*
 - *If an N/A checkbox is not present, or if none of the existing checkboxes apply to your study, you must write in your own justification.*
- *In addition:*
 - *For research where the only study procedures are records/chart review: Sections 6, 21, 22, 24, 25, 26 and 27 do not apply.*
 - *For exempt research: Section 6 may not apply. Section 6.1 will still apply if there is a study intervention.*

Studies with multiple participant groups:

- *If this study involves multiple participant groups (e.g. parents and children), provide information in applicable sections for each participant group. Clearly label responses when they differ. For example:*

Response Example

Intervention Group:

Control Group:

Formatting:

- *Do not remove template instructions or section headings when they do not apply to your study.*

If you are pasting information from other documents using the “Merge Formatting” Paste option will maintain the formatting of the response boxes.

Amendments:

- *When making modifications or revisions to this and other documents, use the **Track Changes** function in Microsoft Word.*
- *Update the version date or number **on Page 3.***

PROTOCOL TITLE:

Include the full protocol title.

Response: Neuromodulation after spinal cord injury to improve limb function

PRINCIPAL INVESTIGATOR:

Name

Department

Telephone Number

Email Address

Response:

Hang Jin Jo

Department of Rehabilitation Science

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VERSION NUMBER/DATE:

Include the version number and date of this protocol.

Response:

Version 5 (11/21/2024)

REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?
1	8/30/2023	Adding rTMS protocols	Yes
2	2/6/2024	Adding long-term stimulation protocol and increase in the number of participants	Yes
3	5/29/2024	1. Modification of stimulation sessions in Study 1 based on preliminary results 2. Use of Buffalo Research Registry	Yes
4	6/14/2024	Clarification of TMS coils used in the protocol. Additional information in the iTBS sessions.	No
5	11/21/2024	Adding a high density EMG system	No

FUNDING:

Indicate any funding for this proposal. This should match the Funding Sources page in Click IRB.

Response:

Dr. Jo's start-up fund will be used for subject payment

GRANT APPLICABILITY:

Indicate whether this protocol is funded by a grant (e.g. NIH, foundation grant). For a grant with multiple aims, indicate which aims are covered by this research proposal.

NOTE: This question does not apply to studies funded by a sponsor contract.

 *Include a copy of the grant proposal with your submission.*

Response: This protocol is not funded by a grant.

RESEARCH REPOSITORY:

Indicate where the research files will be kept, including when the study has been closed. The repository should include, at minimum, copies of IRB correspondence (approval, determination letters) as well as signed consent documents. This documentation should be maintained for 3 years after the study has been closed.

Response:

Location: 522 Kimball

Address: 40 Goodyear Rd, Buffalo, NY 14214

Department: Department of Rehabilitation Science

1.0 Study Summary

Study Title	Neuromodulation after spinal cord injury to improve limb function
Study Design	Randomized controlled design
Primary Objective	To test a strategy to restore upper limb function in individuals with spinal cord injury
Secondary Objective(s)	To study physiological mechanisms of functional recovery in individuals with spinal cord injury
Research Intervention(s)/ Investigational Agent(s)	Intervention includes stimulation of brain and peripheral nerves.
IND/IDE #	
Study Population	Individuals with and without spinal cord injury
Sample Size	60
Study Duration for individual participants	3-4 months
Study Specific Abbreviations/ Definitions	SCI-Spinal cord injury tDCS-transcranial direct current stimulation MEPs- motor evoked potentials TMS-transcranial magnetic stimulation rTMS-repetitive transcranial magnetic stimulation

2.0 Objectives*

2.1 Describe the purpose, specific aims, or objectives of this research.

Response: The main goal of rehabilitation strategies in humans with spinal cord injury (SCI) is to strengthen transmission in spared neural networks to restore functional movements. However, current treatments in SCI result in limited behavioral improvements, highlighting the need to develop new methodologies to strengthen spared neural networks. Recent evidence showed that transmission in late corticospinal descending volleys in humans with SCI play a crucial role in the recruitment of spinal motoneurons and functional outcomes. Therefore, the goal of this proposal is to target late corticospinal descending volleys using neuromodulation after cervical SCI. Recent study showed that motor evoked potentials (MEPs) from TMS in anterior-posterior (AP) direction was particularly altered after SCI reflecting impairments in the late corticospinal descending volleys after SCI. Therefore, we will aim to target late descending corticospinal volleys with neuromodulation. First, we will strengthen the corticospinal motoneuronal connectivity with paired stimulation to increase the output of late corticospinal volleys. We will use TMS in AP direction paired with peripheral nerve stimulation based on spike-timing dependent plasticity. Second, we will investigate how other types of brain stimulation affects neuroplasticity of corticospinal volleys. This will be studied by facilitating corticospinal excitability with repetitive transcranial magnetic stimulation (rTMS) or transcranial direct current stimulation (tDCS). After the effective stimulation parameters are identified, we will apply the stimulation for multiple sessions to explore the long-term effect of the protocol.

2.2 State the hypotheses to be tested, if applicable.

NOTE: A hypothesis is a specific, testable prediction about what you expect to happen in your study that corresponds with your above listed objectives.

Response: It is hypothesized that paired stimulation with AP TMS will facilitate late corticospinal volleys more than early corticospinal volleys and that both rTMS and tDCS can effectively facilitate late corticospinal volleys and potentiate the effect of paired stimulation using AP TMS. It is also hypothesized that there will be cumulative effect with the multiple sessions.

3.0 Scientific Endpoints*

3.1 Describe the scientific endpoint(s), the main result or occurrence under study.

*NOTE: Scientific endpoints are outcomes defined before the study begins to determine whether the objectives of the study have been met and to draw conclusions from the data. Include primary and secondary endpoints. Some example endpoints are: reduction of symptoms, improvement in quality of life, or survival. Your response should **not** be a date.*

Response: The primary outcome measure will be motor evoked potentials (MEP).

Transcranial magnetic stimuli (TMS) will be delivered from a Magstim 200 stimulator (Magstim Company) or PowerMAG unit (Mag & More) through figure-of-eight 70 mm or equivalent coil or a double-cone coil to elicit MEPs. TMS will be delivered to the optimal scalp position for activation of muscles in the limbs. The optimal scalp position will be determined by moving the coil in small steps along the hand/arm representations 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). This optimal position will be marked by Brainsight neuronavigation system (Rogue Research, Inc). The targeted muscles will be the first dorsal interosseous, abductor pollicis brevis, flexor carpi radialis, extensor carpi radialis, biceps and triceps brachii, and deltoid. Stimulation intensity will be decided based on resting (minimum intensity required to induce MEPs greater than 50 μ V in 5/10 consecutive trials at rest) and active (minimum intensity able to evoke an MEP bigger than 200 μ V in 5/10 consecutive trials during 5-10% of maximal voluntary contractions) motor thresholds in each subject. 20-30 MEPs will be average in each coil orientation (Anterior-posterior (AP) direction, posterior-anterior direction (PA), or medio-lateral direction (LM)).

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

A) Cortical connectivity: To assess the connectivity between the other cortical areas (OCA) such as cerebellum, posterior parietal cortex (PPC), dorsal premotor cortex (PMd)) and primary motor cortex, paired-pulse technique that consists of TMS over the other cortical areas 3-7 ms before administering a TMS over the primary motor cortex will be used. Stimulation will be delivered from a Magstim 200 stimulator through 110 mm double-cone coil or a standard 70mm figure-of eight coil, or from a PowerMAG unit through a figure-of-eight D70 coil depending on the proximity of the neuronal targets relative to the coil position.

B) Cortical excitability: to assess cortical changes caused by the intervention on the OCA, paired pulse stimulation will be applied on the motor cortex using two Magstim units (Bistim), interval time between pulses (1ms to 100ms) would determine inhibitory/ excitatory cortical changes as vastly reported in the literature (SICI, LICI, ICF). Single pulses used during the collection of MEPs are used as testing pulses, while the 2nd pulse, called the conditioning pulse, is added some milliseconds before with a priming intensity (80 to 120% of the testing pulse intensity).

While cortical excitability can be measured intracortically using paired pulses delivered through the same coil, another type of paired pulse test called paired associative stimulation (PAS) can be also performed using 2 different coils at 2 different brain locations (e.g., motor cortex and

cerebellum). PAS is performed with a stimulus interval of 3-7 ms between two locations of TMS.

C) Motoneuronal excitability (reflected by F-wave persistence and amplitude): Using supramaximal stimulus intensity (120% of the maximal motor response, M-max; 0.2 ms duration, 40 trials) to the ulnar nerve at the wrist for the first dorsal interosseous, median nerve at the wrist for abductor pollicis brevis, and brachial plexus at the Erb's point for the deltoid and biceps brachii. Stimulation will be delivered using 0.2-1 ms rectangular electrical stimulus (DS7A, Digitimer Ltd.). We will quantify latency, peak-to-peak amplitude of each F-wave, and F-wave persistence (number of F-waves present on each set). In muscles where F-waves are not present, H-reflex will be measured instead.

D) EMG and maximum voluntary contraction (MVC): Individuals will perform a MVC of the targeted muscles (deltoid, biceps brachii, flexor carpi radialis, extensor carpi radialis, first dorsal interosseous, and/or abductor pollicis brevis) through surface electrodes secured to the skin over the belly of each muscle using Delsys wireless EMG system. In a subgroup of participants, in addition to the Delsys wireless EMG, we will also use high-density surface EMG (HD-EMG) system to capture muscle activities at a higher resolution. HD-EMG allows motor unit recording and can potentially better detect muscle responses in people with spinal cord injury compared to the standard surface EMG system. We will use 32-channel textile adhesive EMG patch electrodes (4mm electrode diameter, 8.75mm pitch) connected to a wearable SAGA 64+ amplifier (TMSi, Netherlands). The SAGA 64+ can connect two 32-channel EMG patches which are placed on one of the muscles listed above.

E) Graded Redefined Assessment of Strength, Sensibility and Prehension (GRASSP): GRASSP is an extensive and validated impairment and functional measure which can detect subtle neurologic changes in individuals with SCI. Specifically, it evaluates the domains of sensation, strength, quality of different grip patterns and the ability to complete a variety of functional tasks.

F) Pinch grip and power grip forces: Pinch grip and power grip test will be measured with hand-held dynamometer.

4.0 Background*

4.1 *Provide the scientific or scholarly background, rationale, and significance of the research based on the existing literature and how it will contribute to existing knowledge. Describe any gaps in current knowledge. Include relevant preliminary findings or prior research by the investigator.*

Response: The corticospinal tract plays a crucial role in the voluntary control of movements in animals and humans (Lemon, 2008). When the corticospinal tract is impaired due to an injury to the spinal cord, spared

circuits undergo substantial reorganization in the tract. In humans, some of this reorganization can be measured by using noninvasive TMS with evidence showing that MEPs have delayed latencies and higher thresholds after injury (Ellaway et al., 2007). Evidence also showed that after SCI, the temporal dispersion of descending corticospinal volleys is impaired (Cirillo et al., 2016). Especially, late corticospinal volleys are decreased and delayed in SCI participants compared with controls. Several studies in controls have shown that the direction of TMS induced current in the brain result in corticospinal responses with different characteristics (Di Lazzaro et al. 2012, 2018). One of the prominent differences is that MEPs elicited with the coil in the AP orientation have a longer latency than MEPs elicited with the coil in the posterior-anterior (PA) direction. This latency difference can be contributed to differential recruitment of cortical excitatory inputs; AP orientation preferentially recruit neural structures associated with late corticospinal volleys (Day et al., 2004) and AP MEP is considered as a surrogate measure of late corticospinal volleys (Hamada et al, 2013). In earlier research, PI showed how early and late corticospinal descending volleys change after SCI (Jo et al., 2018). Consistent with paired-pulse facilitation results, AP compared to PA MEPs were particularly impaired after SCI. Late descending volleys are involved in specific voluntary motor behaviors such as hand power grip, motor learning, and plasticity protocols (Federico & Perez, 2017; Hannah & Rothwell, 2017; Long et al. 2017). Therefore, targeting late corticospinal descending volleys could potentially be an effective strategy to promote motor recovery of motor function in individuals with SCI.

Studies in animals and humans have shown that interventions that target residual corticospinal tract connections are critical to increase corticospinal transmission to facilitate functional recovery (Oudega and Perez, 2012). One of these interventions is a noninvasive technique called PCMS, which targets corticospinal-motoneuronal connections to induce plasticity at the spinal cord level and have shown to improve corticospinal function and voluntary motor output in humans with incomplete SCI (Bunday and Perez, 2012a; Urbin et al., 2017; Jo and Perez, 2020). In this paradigm, volleys elicited by TMS over the primary motor cortex are precisely timed to reach the presynaptic terminal of corticospinal neurons in the spinal cord 1-2 ms before antidromic volleys elicited in motor axons by electrical peripheral nerve stimulation (PNS) reach motoneurons. Repeated pairs of presynaptic action potentials arriving prior to post-synaptic depolarizing action potentials during PCMS elicit spike-timing dependent plasticity at spinal synapses and potentiate the synaptic strength. Therefore, we will apply PCMS with TMS in AP direction to strengthen the output of late corticospinal descending volleys.

Additionally, previous literatures suggest that manipulating activity in the other cortical projections (from PPC, PMd, cerebellum) to primary motor cortex influence excitability of corticospinal descending volleys (Goldenkoff et al. 2023; Liao et al. 2024). Cerebellar excitation from

theta-burst stimulation attenuated the stimulation induced plasticity whereas cerebellar inhibition enhanced it (Popa et al., 2012). Similarly, cerebellar tDCS induce a facilitatory or inhibitory effect (Ates et al., 2018; Spampinato et al., 2020; Behrangrad et al., 2022) on corticospinal excitability. Although it remains unclear how this influence is mediated, growing evidence suggest that late corticospinal descending volleys may be specifically modified by changes in cerebellar activity. Therefore, cerebellar tDCS may effectively facilitate late corticospinal volleys in people with SCI and potentiate the effect of paired stimulation using AP TMS.

M1 cortical adaptations after damage in descending and ascending spinal tracks, has an impact in many areas of the brain that are associated with motor planning learning and execution. The cerebellum plays an important role in movement regulation and has been shown to change after SCI, cortical and subcortical cerebellar structures show structural and functional changes after cervical and thoracic SCI (Lei et al., 2020, Zheng et al., 2022). The cerebellar motor pathway has been investigated in electrophysiological studies, activation of the dentato-thalamo-cortical (deep structures) tract using noninvasive brain stimulation (NIBS) increases M1 excitability (Groiss, et al., 2013), while the use of NIBS that affect superficial cortical cerebellar structures (e.g. Purkinje cell activation) in turn cause an overall inhibition of M1. (Holdefer et al., 2000, Stoodley et al., 2010). Although it remains unclear how this influence is mediated, growing evidence suggest that late corticospinal descending volleys may be specifically modified by changes in cerebellar activity. For example, a type of NIBS, specifically, transcranial direct current stimulation (tDCS) applied to the cerebellum influences corticospinal descending volleys that is only apparent in late corticospinal volleys (Hamada et al., 2014, Hannah and Rothwell, 2017).

Several types of NIBS have been explored and compared to elicit motor neuroplasticity stimulating the cerebellar-thalamo-cortical (CTC) pathway, the effects have been classified as excitatory, inhibitory and a combinatory effect of the two, recently a study compared four different types of NIBS (PAS, rTMS, cTBS and tDCS) in a population without neurological disorders and found significantly different excitatory effects of rTMS and inhibitory of PAS, while the difference of tDCS was not significant but present and they found no difference on cTBS (Pauly et al., 2021), this report opens new possibilities to refine NIBS protocols, the authors used tDCS in experiment 1 and showed difference but it was not statistically significant thus decided to exclude tDCS from experiment 2 to then realize that some of the effects of rTMS and PAS were not statistically significant anymore. Adding data from experiments 1 and 2 they showed strong statistical power for both protocols while cTBS was not different from sham. Anodal tDCS has been reported to cause increased excitability of M1, but results seem to be mixed depending on the population, Hannah and Rothwell, 2017 showed differences in firing probabilities in healthy

participants that could be used as a predictive test to define not responders to a specific protocol, others have used AP-LM latency differences as potential predictive values (Wiethoff et al., 2014). Showing the remarkable need to define a biomarker that would help define the state of the nervous system with and without injury to predict the benefit of a potential therapy protocol.

4.2 Include complete citations or references.

Response:

Lemon, R.N., 2008. Descending pathways in motor control. *Annu Rev Neurosci* 31, 195-218.

Ellaway, P.H., Catley, M., Davey, N.J., Kuppuswamy, A., Strutton, P., Frankel, H.L., Jamous, A., Savic, G., 2007. Review of physiological motor outcome measures in spinal cord injury using transcranial magnetic stimulation and spinal reflexes. *J Rehabil Res Dev* 44, 69-76.

Cirillo, J., Calabro, F.J., Perez, M.A., 2016. Impaired Organization of Paired-Pulse TMS-Induced I-Waves After Human Spinal Cord Injury. *Cereb Cortex* 26, 2167-2177.

Di Lazzaro, V., Profice, P., Ranieri, F., Capone, F., Dileone, M., Oliviero, A., Pilato, F., 2012. I wave origin and modulation. *Brain Stimul* 5, 512-525.

Di Lazzaro, V., Rothwell, J., Capogna, M., 2018. Noninvasive Stimulation of the Human Brain: Activation of Multiple Cortical Circuits. *Neuroscientist* 24, 246-260.

Day, B.L., Dressler, D., Maertens de Noordhout, A., Marsden, C.D., Nakashima, K., Rothwell, J.C., Thompson, P.D., 1989. Electric and magnetic stimulation of human motor cortex: surface EMG and single motor unit responses. *J Physiol* 412, 449-473.

Groiss SJ, Ugawa Y. *Cerebellum*. *Handb Clin Neurol*. 2013;116:643-53.

Hamada, M., Murase, N., Hasan, A., Balaratnam, M., Rothwell, J.C., 2013. The role of interneuron networks in driving human motor cortical plasticity. *Cereb Cortex* 23, 1593-1605.

Holdefer RN, Miller LE, Chen LL, Houk JC. Functional connectivity between cerebellum and primary motor cortex in the awake monkey. *J Neurophysiol*. 2000 Jul;84(1):585-90.

Jo, H.J., Di Lazzaro, V., Perez, M.A., 2018. Effect of coil orientation on motor-evoked potentials in humans with tetraplegia. *J Physiol* 596, 4909-4921.

Federico, P., Perez, M.A., 2017. Distinct Corticocortical Contributions to Human Precision and Power Grip. *Cereb Cortex* 27, 5070-5082.

Hannah, R., Rothwell, J.C., 2017. Pulse Duration as Well as Current Direction Determines the Specificity of Transcranial Magnetic Stimulation of Motor Cortex during Contraction. *Brain Stimul* 10, 106-115.

Huang YZ, Edwards MJ, Rounis E, Bhatia KP, Rothwell JC. Theta burst stimulation of the human motor cortex. *Neuron*. 2005 Jan 20;45(2):201-6.

Lei Y, Perez MA. Cerebellar contribution to sensorimotor adaptation deficits in humans with spinal cord injury. *Sci Rep*. 2021 Jan 28;11(1):2507.

Long, J., Federico, P., Perez, M.A., 2017. A novel cortical target to enhance hand motor output in humans with spinal cord injury. *Brain* 140, 1619-1632.

Oudega, M., Perez, M.A., 2012. Corticospinal reorganization after spinal cord injury. *J Physiol* 590, 3647-3663.

Bunday, K.L., Perez, M.A., 2012. Motor recovery after spinal cord injury enhanced by strengthening corticospinal synaptic transmission. *Curr Biol* 22, 2355-2361.

Urbán, M.A., Özdemir, R.A., Tazoe, T., Perez, M.A., 2017. Spike-timing-dependent plasticity in lower-limb motoneurons after human spinal cord injury. *J Neurophysiol* 118, 2171-2180.

Jo, H.J., Perez, M.A., 2020. Corticospinal-motor neuronal plasticity promotes exercise-mediated recovery in humans with spinal cord injury. *Brain* 143, 1368-1382.

Popa, T., Velayudhan, B., Hubsch, C., Pradeep, S., Roze, E., Vidailhet, M., Meunier, S., Kishore, A., 2013. Cerebellar processing of sensory inputs primes motor cortex plasticity. *Cereb Cortex* 23, 305-314.

Ates, M.P., Alaydin, H.C., Cengiz, B., 2018. The effect of the anodal transcranial direct current stimulation over the cerebellum on the motor cortex excitability. *Brain Res Bull* 140, 114-119.

Spampinato, D.A., Celnik, P.A., Rothwell, J.C., 2020. Cerebellar-Motor Cortex Connectivity: One or Two Different Networks? *J Neurosci* 40, 4230-4239.

Behrangrad, S., Zoghi, M., Kidgell, D., Mansouri, F., Jaberzadeh, S., 2022. The effects of concurrent bilateral anodal tDCS of primary motor cortex and cerebellum on corticospinal excitability: a randomized, double-blind sham-controlled study. *Brain Struct Funct* 227, 2395-2408.

Wiethoff S, Hamada M, Rothwell JC. Variability in response to transcranial direct current stimulation of the motor cortex. *Brain Stimul*. 2014 May-Jun;7(3):468-75.

Zheng W, Wang L, Yang B, Chen Q, Hu Y, Du J, Li X, Chen X, Qin W, Li K, Lu J, Chen N. Cerebellum regulating cerebral functional cortex through multiple pathways in complete thoracolumbar spinal cord injury. *Front Neurosci*. 2022 Jul 29;16:914549.

Goldenkoff ER, Deluisi JA, Destiny DP, Lee TG, Michon KJ, Brissenden JA, Taylor SF, Polk TA, Vesia M. The behavioral and neural effects of parietal theta burst stimulation on the grasp network are stronger during a grasping task than at rest. *Front Neurosci*. 2023 Oct 26;17:1198222. doi: 10.3389/fnins.2023.1198222. PMID: 37954875; PMCID: PMC10637360.

Liao WY, Opie GM, Ziemann U, Semmler JG. Modulation of dorsal premotor cortex differentially influences visuomotor adaptation in young and older adults. *Neurobiol Aging*. 2024 May 25;141:34-45. doi: 10.1016/j.neurobiolaging.2024.05.011. Epub ahead of print. PMID: 38815412.

5.0 Study Design*

5.1 *Describe and explain the study design (e.g. case-control, cross-sectional, ethnographic, experimental, interventional, longitudinal, observational).*

Response: Prospective study.

Study 1. Subjects will participate in one or both of the following sessions: (1) rTMS and (2) sham rTMS. Functional and physiological outcomes will be measured before and after each intervention.

Study 2. Subjects will receive the rTMS with motor training for long-term up to 50 sessions. Motor training involves hand motor training.

6.0 Study Intervention/Investigational Agent

6.1 *Describe the study intervention and/or investigational agent (e.g., drug, device) that is being evaluated.*

Response:

Two forms of rTMS (cTBS and iTBS) will be evaluated since they have been reported to have a cortical neuromodulatory effect. Theta burst stimulation (TBS) will be applied over one of the brain regions related to motor control including primary motor cortex (M1), prefrontal cortex (PMd), posterior parietal cortex (PPC), and cerebellum to investigate the effect on M1 excitability. The stimulation intensity will be set at the 80-100% of the resting (RMT) or active motor threshold (AMT). The rTMS protocols are based on previous reports consisting of bursts of pulses containing 3 pulses at 50 Hz (3 pulses per second) repeated at 200 ms intervals (5 Hz). In the intermittent theta burst stimulation pattern (iTBS), a 2 second train of TBS is repeated every 10 seconds (600 pulses for 3 minutes). In a subgroup of participants, iTBS will consist of iTBS on the other cortical areas (PPC, PMd, or cerebellum) followed by iTBS on M1. In the continuous theta burst stimulation paradigm (cTBS), a 40 s train of uninterrupted TBS is given (600 pulses). Sham TBS protocols will be randomly included since they have been reported not to have any plastic effect e.g., intermediate theta burst stimulation (imTBS) where 5 seconds trains of TBS is repeated every 15 seconds for a total of 110 s (600 pulses). Sham coil (Mag&More cooled double coil) can be used for sham rTMS session.

During stimulation session, participants may be asked to contract the arm/hand muscles to perform specific tasks or relax their muscles as much they can. Small light bulbs in different colors placed in front of the participants will cue which motor task they need to perform (e.g. pinch grip with red light or power grip with blue light).

Effective form of rTMS protocol identified from the preliminary data collection will be used for long-term application in study 2. Subjects will receive the rTMS with motor training. Motor training involves either hand motor training or gait training. Hand motor training will focus on strengthening and/or improving coordination to perform motor tasks such as precision/power grip.

6.2 *Drug/Device Handling: If the research involves drugs or device, describe your plans to store, handle, and administer those drugs or devices so that they will be used only on subjects and be used only by authorized investigators.*

- *If the control of the drugs or devices used in this protocol will be accomplished by following an established, approved organizational SOP (e.g., Research Pharmacy SOP for the Control of Investigational Drugs, etc.), please reference that SOP in this section.*

Response: N/A

6.3 *If the drug is investigational (has an IND) or the device has an IDE or a claim of abbreviated IDE (non-significant risk device), include the following information:*

- *Identify the holder of the IND/IDE/Abbreviated IDE.*
- *Explain procedures followed to comply with sponsor requirements for FDA regulated research for the following:*

<i>FDA Regulation</i>	<i>Applicable to:</i>		
	<i>IND Studies</i>	<i>IDE studies</i>	<i>Abbreviated IDE studies</i>
<i>21 CFR 11</i>	<i>X</i>	<i>X</i>	
<i>21 CFR 54</i>	<i>X</i>	<i>X</i>	
<i>21 CFR 210</i>	<i>X</i>		
<i>21 CFR 211</i>	<i>X</i>		
<i>21 CFR 312</i>	<i>X</i>		
<i>21 CFR 812</i>		<i>X</i>	<i>X</i>
<i>21 CFR 820</i>		<i>X</i>	

Response: This trial is not assessing the safety of any of these devices.

7.0 Local Number of Subjects

7.1 *Indicate the total number of subjects that will be enrolled or records that will be reviewed locally.*

Response: 30 individuals with SCI and 30 healthy controls will be enrolled.

7.2 *If applicable, indicate how many subjects you expect to screen to reach your target sample (i.e. your screen failure rate).*

Response: We expect to screen 60 individuals with SCI and 40 individuals with healthy controls.

7.3 *Justify the feasibility of recruiting the proposed number of eligible subjects within the anticipated recruitment period. For example, how many potential subjects do you have access to? What percentage of those potential subjects do you need to recruit?*

Response: We have access to ~170 individuals with SCI in Buffalo area through Buffalo Research Registry who can potentially participate in this study.

8.0 Inclusion and Exclusion Criteria*

8.1 *Describe the criteria that define who will be **included** in your final study sample.*

NOTE: This may be done in bullet point fashion.

Response: Individuals with SCI: (1) Male and females between ages 18-75 years, (2) Chronic SCI (≥ 6 months of injury).

Healthy controls: Male and females between ages 18-75 years.

8.2 *Describe the criteria that define who will be **excluded** from your final study sample.*

NOTE: This may be done in bullet point fashion.

Response: Individuals with SCI: (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 not concurrent with SCI 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 such as antipsychotic drugs (chlorpromazine, clozapine) or tricyclic antidepressants, (8) Pregnant females, and (9) Ongoing cord compression or a syrinx in the spinal cord or who suffer from a spinal cord disease such as spinal stenosis, spinal bifida or herniated disk.

Healthy controls: As above.

8.3 *Indicate specifically whether you will include any of the following special populations in your study using the checkboxes below.*

NOTE: Members of special populations may not be targeted for enrollment in your study unless you indicate this in your inclusion criteria.

Response:

- ☐ Adults unable to consent
- ☐ Individuals who are not yet adults (infants, children, teenagers)

- ☐ Pregnant women
- ☐ Prisoners

8.4 Indicate whether you will include non-English speaking individuals in your study. **Provide justification if you will exclude non-English speaking individuals.**

*In order to meet one of the primary ethical principles of equitable selection of subjects, non-English speaking individuals may **not** be routinely excluded from research as a matter of convenience.*

In cases where the research is of therapeutic intent or is designed to investigate areas that would necessarily require certain populations who may not speak English, the researcher is required to make efforts to recruit and include non-English speaking individuals. However, there are studies in which it would be reasonable to limit subjects to those who speak English. Some examples include pilot studies, small unfunded studies with validated instruments not available in other languages, studies with numerous questionnaires, and some non-therapeutic studies which offer no direct benefit.

Response: I will not include non-English speaking individuals in the study. This study is a small non-therapeutic study which offers no direct benefit to participants, and so it would not inequitably withhold benefit from them.

9.0 Vulnerable Populations*

If the research involves special populations that are considered vulnerable, describe the safeguards included to protect their rights and welfare.

NOTE: You should refer to the appropriate checklists, referenced below, to ensure you have provided adequate detail regarding safeguards and protections. You do not, however, need to provide these checklists to the IRB.

9.1 For research that involves **pregnant women**, safeguards include:
NOTE CHECKLIST: Pregnant Women (HRP-412)

Response:

- ☒ N/A: This research does not involve pregnant women.

9.2 For research that involves **neonates of uncertain viability or non-viable neonates**, safeguards include:

NOTE CHECKLISTS: Non-Viable Neonates (HRP-413), or Neonates of Uncertain Viability (HRP-414)

Response:

☒ **N/A:** This research does not involve non-viable neonates or neonates of uncertain viability.

9.3 For research that involves **prisoners**, safeguards include:

NOTE CHECKLIST: Prisoners (HRP-415)

Response:

☒ **N/A:** This research does not involve prisoners.

9.4 For research that involves **persons who have not attained the legal age for consent to treatments or procedures involved in the research (“children”)**, safeguards include:

NOTE CHECKLIST: Children (HRP-416)

Response:

☒ **N/A:** This research does not involve persons who have not attained the legal age for consent to treatments or procedures (“children”).

9.5 For research that involves **cognitively impaired adults**, safeguards include:

NOTE CHECKLIST: Cognitively Impaired Adults (HRP-417)

Response:

☒ **N/A:** This research does not involve cognitively impaired adults.

9.6 Consider if other specifically targeted populations such as students, employees of a specific firm, or educationally or economically disadvantaged persons are vulnerable. **Provide information regarding their safeguards and protections, including safeguards to eliminate coercion or undue influence.**

Response:

If students currently enrolled in any University at Buffalo course, their grades in any course will not be affected, positively or negatively, based on their participation in this research. If they feel that their academic course grade was adversely impacted by their participation, or lack thereof, the assignment(s) will be regraded by a faculty member not associated with the study.

10.0 Eligibility Screening*

10.1 Describe **screening procedures** for determining subjects’ eligibility.

Screening refers to determining if prospective participants meet inclusion and exclusion criteria.

 Include all relevant screening documents with your submission (e.g. screening protocol, script, questionnaire).

Response: All individuals interested in participating in the study will be scheduled with an initial screening visit. In case an individual makes

initial contact via phone call, we will use phone screening script to ask a few questions before scheduling the initial screening visit. During the initial screening visit, study protocols will be explained in detail and consent form will be obtained. Then, individuals will be carefully screened for the following contraindications to TMS: pacemakers, metal implants in the head region, history of epilepsy or seizures, concussion within the last 6 months, and pregnancy. In addition, demographics and medical history will be collected using the first page of the “Screening form”. An eligible individual after the screening can participate in the study session as their schedule allows. TMS test can be administered to examine the presence and threshold of MEP response from TMS.

In individuals with SCI, during the screening visit, we will confirm with the participant whether they have chronic spinal cord injury and ask their level of injury, cause of injury, time of injury, and ASIA score using the second page of the “Screening Form”. Additionally, a brief TMS test will be administered for individuals with SCI to examine the presence and threshold of MEP response from TMS. This is because the threshold to get a muscle response from TMS typically increases after SCI and we want to make sure that we can get the TMS responses needed for the study.

☐ N/A: There is no screening as part of this protocol.

11.0 Recruitment Methods

☐ N/A: This is a records review only, and subjects will not be recruited. NOTE: If you select this option, please make sure that all records review procedures and inclusion/exclusion screening are adequately described in other sections.

11.1 Describe when, where, and how potential subjects will be recruited.

NOTE: Recruitment refers to how you are identifying potential participants and introducing them to the study. Include specific methods you will use (e.g. searching charts for specific ICD code numbers, Research Participant Groups, posted advertisements, etc.).

Response: First, this study will be publicized on the UB Participate in Research (PIR) portal (www.research.buffalo.edu/portal/clinicaltrial/) while in the active recruitment period. Once study accruals have been met, the study will be removed from the portal. A lay title and study description will be included on the portal and have been included as an attachment in Click for approval. Once approval is received, the study will be populated onto the portal and will receive its own unique hyperlink. The UB PIR Portal was determined to be not research involving human subjects.

Second, the Clinical and Translational Science Institute’s (CTSI) Community Engagement Team (CET) hosts the Buffalo Research Registry (BRR, IRB Approved STUDY00000806), a resource that connects researchers looking to recruit participants and community members looking to get involved with research. To participate in the registry, volunteers complete a voluntary intake

form. Volunteers have agreed to be contacted about potential research opportunities based on their self-reported information.

As described in the BRR's IRB Approved Protocol (STUDY00000806), key personnel from the CTSI will serve as the conduit between our research team and the registry volunteers. Key personnel will verify our IRB study approval, review inclusion and exclusion criteria and will sort the registry data accordingly.

In terms of recruiting for our study, key personnel will pull volunteer reports using the inclusion and exclusion criteria. Key personnel will centrally invite volunteers to participate in the study and provide a warm hand off to our team. There are two ways we are sharing our study. These include:

Electronically- Using the volunteer report from REDCap, key personnel from the CTSI will send initial e-mail invites to introduce our study to registry volunteers.

Post Mail- Key personnel from the CTSI will provide our team with contact information (i.e. first name, last name, post mail address) to prepare a mailing. This information will be shared in a password protected excel spread sheet. The password to the spreadsheet will be sent in a separate follow-up e-mail. We will only use the list for this protocol and we agree to destroy the list once recruitment for the study has closed.

We also plan on conducting follow-up by phone/email after initial contact. This contact information will be provided in a password protected excel spread sheet. The password to the spreadsheet will be sent in a separate follow-up e-mail. We will only use the list for this protocol and we agree to destroy the list once recruitment for the study has closed.

We will have no access to the health information provided in the registry.

Lastly, study flyers will be placed at the buildings at UB Campuses to recruit control subjects. The study flyer will be also posted at the Motion Project and other local clinics where it is allowed to recruit participants with SCI as well as community settings. Name and contact information of the PI or research scientist are listed on the flyer.

11.2 Describe how you will protect the privacy interests of prospective subjects during the recruitment process.

NOTE: Privacy refers to an individual's right to control access to him or herself.

Response: Research procedures will be conducted by approved members of the research team in private areas. Information to be collected will be limited to the amount necessary to complete research specific aims and study goals.

11.3 Identify any materials that will be used to recruit subjects.

NOTE: Examples include scripts for telephone calls, in person announcements / presentations, email invitations.

 *For advertisements, include the final copy of printed advertisements with your submission. When advertisements are taped for broadcast, attach the final*

audio/video tape. *NOTE: You may submit the wording of the advertisement prior to taping to ensure there will be no IRB-required revisions, provided the IRB also reviews and approves the final version.*

Response: Our methods of recruitment include posting study flyer, use of Buffalo Research Registry and listing our study at Participate in research portal. Please find the following files included in our submission: Final copy of printed advertisement (“study flyer” and “Study flyer for older adults”) and the content to be listed on Participate in Research Portal (“Participate in Research Portal Listing”). We made a “Study flyer for older adults” to facilitate recruiting age-matched older control participants to SCI group because majority of the control participants contacting us will be young students at UB. We will post this flyer for older adults at local community settings.

12.0 Procedures Involved*

12.1 *Provide a description of **all research procedures or activities** being performed and when they are performed once a subject is screened and determined to be eligible. Provide as much detail as possible.*

NOTE: This should serve as a blueprint for your study and include enough detail so that another investigator could pick up your protocol and replicate the research. For studies that have multiple or complex visits or procedures, consider the addition of a schedule of events table in in your response.

Response: Relevant medical history will be asked to the participants during the screening and no medical records will be obtained from charts. Once screening is done and if the participant is eligible for the study, the participant will be asked to complete two sessions separated by at least 2-3 days. The two sessions are the following: (1) rTMS and (2) sham rTMS

MRI will be collected during the study in a subset of participants if needed for the following purposes; first, to evaluate the spinal cord injury level and specific characteristics of the injury and second, to render 3 dimensional views of the brain cortex and head scalp to achieve TMS neuronavigation guided accuracy. Target regions for cerebellar and M1 areas will be identified anatomically by using an individual T1-weighted MRI if available. The location of M1 will be electrophysiologically verified by identifying the hot spot where the TMS pulse generates the highest MEP.

At the beginning of each session, and depending on each protocol, EMG electrodes will be placed on the targeted muscles (selected from deltoid, biceps brachii, flexor and extensor carpi radialis, first dorsal interosseous, and abductor pollicis brevis) through surface electrodes secured to the skin over the belly of each muscle. Before and after stimulation, functional and physiological measurements will be performed. Physiological measurements will include:

1) MEPs: TMS will be delivered to the optimal scalp position for activation of hand muscles. This optimal position will be marked by

Brainsight neuronavigation system to ensure that we measure at the same location for pre- and post-measurements. First, resting (minimum intensity required to induce MEPs greater than 50 μ V in 5/10 consecutive trials at rest), and active (minimum intensity able to evoke an MEP bigger than 200 μ V in 5/10 consecutive trials during 5-10% of maximal voluntary contractions) motor thresholds will be determined. Then, 20-30 MEPs will be acquired in each coil orientation (Anterior-posterior (AP), posterior-anterior (PA), and latero-medial (LM) directions) at 110-150% of resting motor threshold intensity.

2) Cerebellar connectivity: To assess the connectivity between the cerebellum and primary motor cortex, paired-pulse technique that consists of TMS over the cerebellum 3-7 ms before administering a TMS over the primary motor cortex will be used. Stimulation will be applied using a Magstim 200 stimulator through 110 mm double-cone coil or figure-of-eight coil and /or a aPowerMAG unit through a figure-of-eight D70 coil.

3) Cortical excitability: to assess cortical changes caused by the intervention on the cerebellar-motor system, paired pulse stimulation will be applied on the motor cortex using two Magstim units (Bistim), interval time between pulses (1ms to 100ms) would determine inhibitory/excitatory cortical changes as vastly reported in the literature (SICI, LICI, ICF). Single pulses used during the collection of MEPs are used as testing pulses, while the 2nd pulse, called the conditioning pulse, is added some milliseconds before with a priming intensity (80 to 120% of the testing pulse intensity).

While cortical excitability can be measured intracortically using paired pulses delivered through the same coil, another type of paired pulse test called paired associative stimulation (PAS) can be also performed using 2 different coils at 2 different brain locations (e.g., motor cortex and cerebellum). PAS is performed with a stimulus interval of 3-7 ms between two locations of TMS.

4) M-max/ F-wave/ H-reflex: Maximal motor response (M-max) will be measured at 0.2 ms duration for first dorsal interosseous, abductor pollicis brevis, deltoid and biceps brachii. For F-wave, supramaximal stimulus intensity (120% of the M-max; 40-60 trials) will be used 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, tibial nerve for soleus, and common peroneal nerve for tibialis anterior. Stimulation will be delivered using 0.2-1 ms rectangular electrical stimulus. We will quantify latency, peak-to-peak amplitude of each F-wave, and F-wave persistence. In muscles where F-waves are not elicited, we will measure H-reflex. 5) EMG and maximum voluntary contraction (MVC): Individuals will perform a MVC of the targeted muscles (deltoid, biceps brachii, first dorsal interosseous, and/or abductor pollicis brevis) through surface electrodes secured to the skin over the belly of each muscle using Delsys

wireless EMG system or HD-EMG system. Testing using HD-EMG system will be additionally completed in the next 10 control subjects and 10 SCI subjects. Physiological measurements will be performed with wireless EMG first, then collected additionally with HD-EMG system at baseline measurements. To minimize the time for EMG placement, we will measure with HD-EMG system first after the neuromodulation, then measure with wireless EMG after.

Functional measurements will be selected from the following measurements depending on the targeted muscle and the level of participant's motor function:

- 1) Graded Redefined Assessment of Strength, Sensibility and Prehension (GRASSP): GRASSP is an extensive and validated impairment and functional measure which can detect subtle neurologic changes in individuals with SCI. Specifically, it evaluates the domains of sensation, strength, quality of different grip patterns and the ability to complete a variety of functional tasks.
- 2) Pinch grip and power grip forces: Pinch grip and power grip test will be measured with hand-held dynamometer.

The stimulation protocol will involve rTMS as described below.

Two forms of rTMS (cTBS and iTBS) will be evaluated since they have been reported to have a cortical neuromodulatory effect. Theta burst stimulation (TBS) will be applied over one of the brain regions related to motor control including primary motor cortex (M1), prefrontal cortex, posterior parietal cortex, and cerebellum to investigate the effect on M1 excitability. The stimulation intensity will be set at the 80-100% of the resting (RMT) or active motor threshold (AMT). The rTMS protocols are based on previous reports consisting of bursts of pulses containing 3 pulses at 50 Hz (3 pulses per second) repeated at 200 ms intervals (5 Hz). In the intermittent theta burst stimulation pattern (iTBS), a 2 second train of TBS is repeated every 10 seconds (600 pulses in 190 seconds). In the continuous theta burst stimulation paradigm (cTBS), a 40 s train of uninterrupted TBS is given (600 pulses). Sham TBS protocols will be randomly included since they have been reported not to have any plastic effect e.g., intermediate theta burst stimulation (imTBS) where 5 seconds trains of TBS is repeated every 15 seconds for a total of 110 s (600 pulses). Alternatively, sham coil (Mag&More cooled double coil) can be used for sham rTMS session.

During any stimulation session, participants may be asked to contract the arm/hand muscles to perform specific tasks or relax their muscles as much they can. Small light bulbs in different colors placed in front of the participants will cue which motor task they need to perform (e.g. pinch grip with red light or power grip with blue light).

Motor training sessions will be provided in study 2. The training will be focused on participant's hand motor function such as grasping function.

In study 1, functional and physiological measurements will be performed before and after each session. In study 2, functional and physiological measurements will be performed at baseline and after every 5-10 sessions.

The testing and/or stimulation session will be stopped at any point if the subject requests. If any of the above testing and/or stimulation session was not completed within one study visit due to unexpected reasons or time constraints, a session can be rescheduled and repeated.

12.2 Describe what data will be collected.

NOTE: For studies with multiple data collection points or long-term follow up, consider the addition of a schedule or table in your response.

Response: During the screening visit, we will obtain a consent form, document demographics and medical history. For SCI participants, we will confirm with the participant whether they have chronic spinal cord injury and ask their level of injury, cause of injury, time of injury, and ASIA score if available. Screening form will be used to collect these data.

Physiological data will be collected via Signal software. Additionally, functional data will be collected by using GRASSPand hand held dynamometer.

12.3 List any instruments or measurement tools used to collect data (e.g. questionnaire, interview guide, validated instrument, data collection form).

Include copies of these documents with your submission.

Response: Screening Form will be used to collect demographic data and medical history, and information regarding voluntary movement and MEP presence in individuals with SCI. All the physiological measurement mentioned in 12.1 will be collected via Signal software and we will use the lab notebook to keep track of file name and the measurement that was done. We will note the name of the Signal files and brief description of what was measured on that file. After data is processed through Signal software, we will keep the physiological and functional outcome measures in the "Data" excel file.

12.4 Describe any source records that will be used to collect data about subjects (e.g. school records, electronic medical records).

Response: N/A

*12.5 Indicate whether or not **individual** subject results, such as results of investigational diagnostic tests, genetic tests, or incidental findings will be shared with subjects or others (e.g., the subject's primary care physician) and if so, describe how these will be shared.*

Response: Individual results will not be shared.

12.6 Indicate whether or not **study** results will be shared with subjects or others, and if so, describe how these will be shared.

Response: De-identified data from this study may be shared with the research community at large to advance science and health. We will remove or code any personal information before results are shared.

13.0 Study Timelines*

13.1 Describe the anticipated duration needed to enroll all study subjects.

Response: We anticipate approximately 2 years to enroll all study subjects.

13.2 Describe the duration of an individual subject's participation in the study. Include length of study visits, and overall study follow-up time.

Response: There will be a 30-60 minute-screening session prior to study sessions. For study 1, there will be up to 2 study sessions in total. Each session will be separated from the previous session for at least 2-3 days. Therefore, an individual subject is expected to participate in the study for a week or longer, depending on their availability. For study 2, there will be up to 50 sessions in total. Participants may have up to 5 sessions/week depending on their availability. Each session will take 2-3 hours

13.3 Describe the estimated duration for the investigators to complete this study (i.e. all data is collected and all analyses have been completed).

Response: We anticipate 2-3 years in total.

14.0 Setting

14.1 Describe all facilities/sites where you will be conducting research procedures. Include a description of the security and privacy of the facilities (e.g. locked facility, limited access, privacy barriers). Facility, department, and type of room are relevant. Do not abbreviate facility names.

NOTE: Examples of acceptable response may be: "A classroom setting in the Department of Psychology equipped with a computer with relevant survey administration software," "The angiogram suite at Buffalo General Medical Center, a fully accredited tertiary care institution within New York State with badge access," or, "Community Center meeting hall."

Response: The study will be conducted at a laboratory space located at the Department of Rehabilitation Science on the first floor of Kimball Tower. The laboratory is equipped with a computer and other equipment such as stimulators and EMG recording setups. In addition, research staff will use an office setting in the Department of Rehabilitation Science on the fifth floor of Kimball Tower, and store any study documents in a secure cabinet. Both laboratory and office will be locked when not occupied.

14.2 For research conducted outside of UB and its affiliates, describe:

- Site-specific regulations or customs affecting the research
- Local scientific and ethical review structure

NOTE: This question is referring to UB affiliated research taking place outside UB, i.e. research conducted in the community, school-based research, international research, etc. It is not referring to multi-site research. UB affiliated institutions include Kaleida Health, ECMC, and Roswell Park Cancer Institute.

Response:

- ☒ N/A: This study is not conducted outside of UB or its affiliates.

15.0 Community-Based Participatory Research

15.1 Describe involvement of the community in the design and conduct of the research.

NOTE: Community-Based Participatory Research (CBPR) is a collaborative approach to research that equitably involves all partners in the research process and recognizes the unique strengths that each brings. CBPR begins with a research topic of importance to the community, has the aim of combining knowledge with action and achieving social change to improve health outcomes and eliminate health disparities.

Response:

- ☒ N/A: This study does not utilize CBPR.

15.2 Describe the composition and involvement of a community advisory board.

Response:

- ☒ N/A: This study does not have a community advisory board.

16.0 Resources and Qualifications

16.1 Describe the qualifications (e.g., education, training, experience, expertise, or certifications) of the Principal Investigator **and** staff to perform the research. When applicable describe their knowledge of the local study sites, culture, and society. Provide enough information to convince the IRB that you have qualified staff for the proposed research.

NOTE: If you specify a person by name, a change to that person will require prior approval by the IRB. If you specify a person by role (e.g., coordinator, research assistant, co-investigator, or pharmacist), a change to that person will not usually

require prior approval by the IRB, provided that the person meets the qualifications described to fulfill their roles.

Response: PI has conducted human research related to movement and physiology for past 15 years. For past 7 years, she has done SCI research using neuromodulation techniques and worked with patients with SCI at various settings such as Miami Project to Cure Paralysis and Shirley Ryan AbilityLab. PI has her education background in physical therapy and is currently a licensed PT in New York State. There will be a postdoc working with PI who also has extensive experience working with SCI patients and neurostimulation.

Describe other resources available to conduct the research.

16.2 Describe the time and effort that the Principal Investigator and research staff will devote to conducting and completing the research.

NOTE: Examples include the percentage of Full Time Equivalents (FTE), hours per week. The question will elicit whether there are appropriate resources to conduct the research.

Response: Principal investigator will work on this project for about 20% and a research scientist will work full time on this project. Student researchers involved in this project will work approximately 9 hours/week.

16.3 Describe the availability of medical or psychological resources that subjects might need as a result of anticipated consequences of the human research, if applicable.

NOTE: One example includes: on-call availability of a counselor or psychologist for a study that screens subjects for depression.

Response: N/A

16.4 Describe your process to ensure that all persons assisting with the research are adequately informed about the protocol, the research procedures, and their duties and functions.

Response: When PI works with research scientist or undergraduate/graduate student on this project, PI will make sure they read and fully understand the protocol, research procedure, and their duties. PI will take her time to explain and practice the research procedure with them before they start working on the study and present at testing sessions whenever needed.

17.0 Other Approvals

17.1 Describe any approvals that will be obtained prior to commencing the research (e.g., school, external site, funding agency, laboratory, radiation safety, or biosafety).

Response:

☒ N/A: This study does not require any other approvals.

18.0 Provisions to Protect the Privacy Interests of Subjects

18.1 *Describe how you will protect subjects' privacy interests during the course of this research.*

NOTE: Privacy refers to an individual's right to control access to him or herself. Privacy applies to the person. Confidentiality refers to how data collected about individuals for the research will be protected by the researcher from release. Confidentiality applies to the data.

Examples of appropriate responses include: "participant only meets with a study coordinator in a classroom setting where no one can overhear", or "the participant is reminded that they are free to refuse to answer any questions that they do not feel comfortable answering."

Response: Research procedure will be conducted in private areas such as closed laboratory space. Information collected will be limited to the amount necessary and specified in this submission to complete research specific aims and study goals.

18.2 *Indicate how the research team is permitted to access any sources of information about the subjects.*

*NOTE: Examples of appropriate responses include: school permission for review of records, consent of the subject, HIPAA waiver. This question **does apply** to records reviews.*

Response: Research team is permitted to access information about the subjects when consented to by the subject.

19.0 Data Management and Analysis*

19.1 *Describe the data analysis plan, including any statistical procedures. This section applies to both quantitative and qualitative analysis.*

Response: Repeated-measures ANOVA and Tukey post hoc analysis will determine effects of GROUP (rTMS and sham rTMS) and TIME (before, after) on physiological outcomes.

19.2 *If applicable, provide a power analysis.*

NOTE: This may not apply to certain types of studies, including chart/records reviews, survey studies, or observational studies. This question is asked to elicit whether the investigator has an adequate sample size to achieve the study objectives and justify a conclusion.

Response: For alpha (type I error) of 0.05 and 1-beta (power) of 0.8, SCI participants (15/group) will be included.

19.3 Describe any procedures that will be used for quality control of collected data.

Response: All physiological measurements will be analyzed by skilled research staff or principal investigator.

20.0 Confidentiality*

A. Confidentiality of Study Data

*Describe the local procedures for maintenance of confidentiality of **study data** and any records that will be reviewed for data collection.*

*20.1 A. Where and how will all data and records be stored? Include information about: password protection, encryption, physical controls, authorization of access, and separation of identifiers and data, as applicable. Include physical (e.g. paper) **and** electronic files.*

Response: 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. Hard/paper copies of the information collected during the screening will be stored in a secured location. All the physiological data collected from Signal software will be stored on restricted access with password protected server (UB Box). These data will be coded with the study number, which may include participants' initials.

20.2 A. How long will the data be stored?

Response: IRB correspondence (approval, determination letters) as well as any signed consent documents will be maintained for at least 3 years after the study has been closed.

Any master list/code key containing patient identifiers should be deleted at the first available opportunity after it is no longer necessary to conduct the research.

Signal data files that contain no identifiable information may be kept indefinitely or deleted. Signal files contain EMG recordings and can be opened with Signal software used for data collection.

Different types of datasets should be handled differently, in accordance with these guidelines. Please describe in this section how each dataset on this study will be stored; this applies to both electronic and paper records.

20.3 A. *Who will have access to the data?*

Response: Only approved members of the research team such as principal investigator, research staff, and students will have access to the data.

20.4 A. *Who is responsible for receipt or transmission of the data?*

Response: Each individual who obtained data from study subject is responsible for receipt or transmission of the data.

20.5 A. *How will the data be transported?*

Response: Data files will be transported from computer that data was collected to the server (UB Box) directly.

B. Confidentiality of Study Specimens

*Describe the local procedures for maintenance of confidentiality of **study specimens**.*

☒ N/A: No specimens will be collected or analyzed in this research.
(Skip to Section 21.0)

20.6 B. *Where and how will all specimens be stored? Include information about: physical controls, authorization of access, and labeling of specimens, as applicable.*

Response:

20.7 B. *How long will the specimens be stored?*

Response:

20.8 B. *Who will have access to the specimens?*

Response:

20.9 B. *Who is responsible for receipt or transmission of the specimens?*

Response:

20.10 B. *How will the specimens be transported?*

Response:

21.0 Provisions to Monitor the Data to Ensure the Safety of Subjects*

- ☐ **N/A:** This study is not enrolling subjects, or is limited to records review procedures only. This section does not apply.

NOTE: *Minimal risk studies may be required to monitor subject safety if the research procedures include procedures that present unique risks to subjects that require monitoring. Some examples include: exercising to exertion, or instruments that elicit suicidality or substance abuse behavior. In such cases, N/A is not an acceptable response.*

21.1 Describe the plan to periodically evaluate the data collected regarding both harms and benefits to determine whether subjects remain safe.

Response: Collected data will include demographic information of subjects and physiological data. We do not anticipate any harms for subject's safety with respect to our data. However, we will address any untoward events during lab weekly lab meetings.

21.2 Describe what data are reviewed, including safety data, untoward events, and efficacy data.

Response: Untoward events will be reviewed if applicable.

21.3 Describe any safety endpoints.

Response: N/A

21.4 Describe how the safety information will be collected (e.g., with case report forms, at study visits, by telephone calls with participants).

Response: Any safety related information or feedback from subjects will be collected during study visits.

21.5 Describe the frequency of safety data collection.

Response: We will check the subject's status before, after, and during the whole time while subject is in the study session.

21.6 Describe who will review the safety data.

Response: Principal investigator will review any safety issues/concerns reported by subjects and/or study team.

21.7 Describe the frequency or periodicity of review of cumulative safety data.

Response: There will be no physical cumulative safety data, but any note/report will be reviewed at least weekly.

21.8 Describe the statistical tests for analyzing the safety data to determine whether harm is occurring.

Response: We do not foresee any measurable harmfulness to the subjects.

21.9 Describe any conditions that trigger an immediate suspension of the research.

Response: N/A

22.0 Withdrawal of Subjects*

☐ N/A: This study is not enrolling subjects. This section does not apply.

*22.1 Describe **anticipated** circumstances under which subjects may be withdrawn from the research without their consent.*

Response: Subjects may be withdrawn from the research without their consent if any of the inclusion criteria ceases to be valid or if any exclusion criteria will manifest after enrollment.

22.2 Describe any procedures for orderly termination.

NOTE: Examples may include return of study drug, exit interview with clinician. Include whether additional follow up is recommended for safety reasons for physical or emotional health.

Response: N/A

22.3 Describe procedures that will be followed when subjects withdraw from the research, including retention of already collected data, and partial withdrawal from procedures with continued data collection, as applicable.

Response: We will retain already collected data if participant's permission could be obtained.

23.0 Risks to Subjects*

23.1 *List the reasonably foreseeable risks, discomforts, hazards, or inconveniences to the subjects related to their participation in the research. Consider physical, psychological, social, legal, and economic risks. Include a description of the probability, magnitude, duration, and reversibility of the risks.*

NOTE: Breach of confidentiality is always a risk for identifiable subject data.

Response:

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.

Peripheral Nerve Stimulation: 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.

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. 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. 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.

Breach of Confidentiality

23.2 *Describe procedures performed to lessen the probability or magnitude of risks, including procedures being performed to monitor subjects for safety.*

Response: EMG: We will clean the area with alcohol and use standard, hospital grade electrodes.

Peripheral Nerve Stimulation: Skin irritation will be minimized by cleaning the skin with alcohol before and after the application of the electrodes.

TMS procedures: 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. If a headache or mild scalp discomfort occurs, subjects will be directed to use over the counter pain medication at their own discretion. An authorized study team member will be present during all TMS procedures. If a participant has a seizure during the procedure, we will immediately call 911.

Breach of Confidentiality: See section 20.

This study also involves the possibility of 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.

23.3 *If applicable, indicate **which procedures** may have risks to the subjects that are currently unforeseeable.*

Response: N/A

23.4 *If applicable, indicate which research procedures may have risks to an embryo or fetus should the subject be or become pregnant.*

Response: N/A

23.5 *If applicable, describe risks to others who are not subjects.*

Response: N/A

24.0 Potential Benefits to Subjects*

24.1 *Describe the potential benefits that individual subjects may experience by taking part in the research. Include the probability, magnitude, and duration of the potential benefits. Indicate if there is no direct benefit.*

*NOTE: Compensation **cannot** be stated as a benefit.*

Response: Participation in the experiment may result in no direct improvement.

25.0 Compensation for Research-Related Injury

- ☐ N/A: The research procedures for this study do not present risk of research related injury (e.g. survey studies, records review studies). This section does not apply.

25.1 *If the research procedures carry a risk of research related injury, describe the available compensation to subjects in the event that such injury should occur.*

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

25.2 *Provide a copy of contract language, if any, relevant to compensation for research related injury.*

NOTE: *If the contract is not yet approved at the time of this submission, submit the current version here. If the contract is later approved with **different language regarding research related injury**, you must modify your response here and submit an amendment to the IRB for review and approval.*

Response: N/A

26.0 Economic Burden to Subjects

26.1 *Describe any costs that subjects may be responsible for because of participation in the research.*

NOTE: *Some examples include transportation or parking.*

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

☐ N/A: This study is not enrolling subjects, or is limited to records review procedures only. This section does not apply.

27.0 Compensation for Participation

27.1 *Describe the amount and timing of any compensation to subjects, including monetary, course credit, or gift card compensation.*

Response: Participants will be paid \$10/hour for your time and effort. Each session is anticipated to last 1-3 hours.

☐ N/A: This study is not enrolling subjects, or is limited to records review procedures only. This section does not apply.

☐ N/A: There is no compensation for participation. This section does not apply.

28.0 Consent Process

28.1 *Indicate whether you will be obtaining consent.*

NOTE: *This does not refer to consent documentation, but rather whether you will be obtaining permission from subjects to participate in a research study. Consent documentation is addressed in Section 29.0.*

- ☒ **Yes** (If yes, Provide responses to each question in this Section)
☐ **No** (If no, Skip to Section 29.0)

28.2 Describe where the consent process will take place. Include steps to maximize subjects' privacy.

Response: The consent process will take place at closed laboratory space and be conducted only by approved members of the research team.

28.3 Describe how you will ensure that subjects are provided with a sufficient period of time to consider taking part in the research study.

NOTE: It is always a requirement that a prospective subject is given sufficient time to have their questions answered and consider their participation. See "SOP: Informed Consent Process for Research (HRP-090)" Sections 5.5 and 5.6.

Response: Subjects will be given or sent a copy of the Informed Consent form to be read before the consenting procedure begins to provide them enough time in advance. When the subject (and 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. Subjects will be invited and encouraged to take the written information home to consider the information and discuss the decision with family members and others before making a decision.

28.4 Describe any process to ensure ongoing consent, defined as a subject's willingness to continue participation for the duration of the research study.

Response: Even after a subject is consented, during the experiment, we will ask subject's willingness to continue for each process/test.

28.5 Indicate whether you will be following "SOP: Informed Consent Process for Research (HRP-090)." Pay particular attention to Sections 5.4-5.9. If not, or if there are any exceptions or additional details to what is covered in the SOP, describe:

- The role of the individuals listed in the application who are involved in the consent process
- The time that will be devoted to the consent discussion
- Steps that will be taken to minimize the possibility of coercion or undue influence
- Steps that will be taken to ensure the subjects' understanding

Response:

- ☒ We have reviewed and will be following “SOP: Informed Consent Process for Research (HRP-090).”

Non-English Speaking Subjects

- ☒ **N/A:** This study will not enroll Non-English speaking subjects.
(Skip to Section 28.8)

28.6 *Indicate which language(s) other than English are likely to be spoken/understood by your prospective study population or their legally authorized representatives.*

NOTE: The response to this Section should correspond with your response to Section 8.4 of this protocol.

Response: N/A

28.7 *If subjects who do not speak English will be enrolled, describe the process to ensure that the oral and written information provided to those subjects will be in that language, how you will ensure that subjects are provided with a sufficient period of time to consider taking part in the research study, and any process to ensure ongoing consent. Indicate the language that will be used by those obtaining consent.*

NOTE: Guidance is provided on “SOP: Informed Consent Process for Research (HRP-090).”

Response: N/A

Cognitively Impaired Adults

- ☒ **N/A:** This study will not enroll cognitively impaired adults.
(Skip to Section 28.9)

28.8 *Describe the process to determine whether an individual is capable of consent.*

Response: N/A

Adults Unable to Consent

- ☒ **N/A:** This study will not enroll adults unable to consent.
(Skip to Section 28.13)

When a person is not capable of consent due to cognitive impairment, a legally authorized representative should be used to provide consent (Sections 28.9 and

28.10) and, where possible, assent of the individual should also be solicited (Sections 28.11 and 28.12).

28.9 Describe how you will identify a Legally Authorized Representative (LAR). Indicate that you have reviewed the “SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)” for research in New York State.

NOTE: Examples of acceptable response includes: verifying the electronic medical record to determine if an LAR is recorded.

Response:

☐ We have reviewed and will be following “SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013).”

28.10 For research conducted outside of New York State, provide information that describes which individuals are authorized under applicable law to consent on behalf of a prospective subject to their participation in the research. One method of obtaining this information is to have a legal counsel or authority review your protocol along with the definition of “legally authorized representative” in “SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013).”

Response:

28.11 Describe the process for assent of the adults:

- *Indicate whether assent will be obtained from all, some, or none of the subjects. If some, indicate which adults will be required to assent and which will not.*

Response:

- *If assent will not be obtained from some or all subjects, provide an explanation of why not.*

Response:

28.12 Describe whether assent of the adult subjects will be documented and the process to document assent.

NOTE: The IRB allows the person obtaining assent to document assent on the consent document using the “Template Consent Document (HRP-502)” Signature Block for Assent of Adults who are Legally Unable to Consent.

Response:

Subjects who are not yet Adults (Infants, Children, and Teenagers)

- ☒ **N/A:** This study will not enroll subjects who are not yet adults.
(Skip to Section 29.0)

28.13 Describe the criteria that will be used to determine **whether a prospective subject has not attained the legal age for consent to treatments or procedures involved in the research** under the applicable law of the jurisdiction in which the research will be conducted (**e.g., individuals under the age of 18 years**). For research conducted in NYS, review “SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)” to be aware of which individuals in the state meet the definition of “children.”

NOTE: Examples of acceptable responses include: verification via electronic medical record, driver’s license or state-issued ID, screening questionnaire.

Response:

28.14 **For research conducted outside of New York State**, provide information that describes which persons have not attained the legal age for consent to treatments or procedures involved the research, under the applicable law of the jurisdiction in which research will be conducted. One method of obtaining this information is to have a legal counsel or authority review your protocol along the definition of “children” in “SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013).”

Response:

28.15 Describe whether parental permission will be obtained from:

Response:

- ☐ One parent even if the other parent is alive, known, competent, reasonably available, and shares legal responsibility for the care and custody of the child.
- ☐ Both parents unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.
- ☐ Parent permission will not be obtained. A waiver of parent permission is being requested.

NOTE: The requirement for parent permission is a protocol-specific determination made by the IRB based on the risk level of the research. For guidance, review the “CHECKLIST: Children (HRP-416).”

28.16 Describe whether permission will be obtained from individuals **other than parents**, and if so, who will be allowed to provide permission. Describe your procedure for determining an individual's authority to consent to the child's general medical care.

Response:

28.17 Indicate whether assent will be obtained from all, some, or none of the **children**. If assent will be obtained from some children, indicate which children will be required to assent.

Response:

28.18 When assent of children is obtained, describe how it will be documented.

Response:

29.0 Waiver or Alteration of Consent Process

Consent will not be obtained, required information will not be disclosed, or the research involves deception.

☒ N/A: A waiver or alteration of consent is not being requested.

29.1 If the research involves a waiver or alteration of the consent process, please review the "CHECKLIST: Waiver or Alteration of Consent Process (HRP-410)" to ensure that you have provided sufficient information for the IRB to make the determination that a waiver or alteration can be granted.

NOTE: For records review studies, the first set of criteria on the "CHECKLIST: Waiver or Alteration of Consent Process (HRP-410)" applies.

Response:

29.2 If the research involves a waiver of the consent process for planned emergency research, please review the "CHECKLIST: Waiver of Consent for Emergency Research (HRP-419)" to ensure you have provided sufficient information for the IRB to make these determinations. Provide any additional information necessary here:

Response:

30.0 Process to Document Consent

☐ N/A: A Waiver of Consent is being requested.
(Skip to Section 31.0)

30.1 *Indicate whether you will be following “SOP: Written Documentation of Consent (HRP-091).” If not or if there are any exceptions, describe whether and how consent of the subject will be obtained including whether or not it will be documented in writing.*

NOTE: If your research presents no more than minimal risk of harm to subjects and involves no procedures for which written documentation of consent is normally required outside of the research context, the IRB will generally waive the requirement to obtain written documentation of consent. This is sometimes referred to as ‘verbal consent.’ Review “CHECKLIST: Waiver of Written Documentation of Consent (HRP-411)” to ensure that you have provided sufficient information.

 *If you will document consent in writing, attach a consent document with your submission. You may use “TEMPLATE CONSENT DOCUMENT (HRP-502)”. If you will obtain consent, but not document consent in writing, attach the script of the information to be provided orally or in writing (i.e. consent script or Information Sheet).*

Response:

- ☒ We will be following “SOP: Written Documentation of Consent” (HRP-091).

31.0 Multi-Site Research (Multisite/Multicenter Only)*

- ☒ N/A: This study is not an investigator-initiated multi-site study. This section does not apply.

31.1 *Indicate the total number of subjects that will be enrolled or records that will be reviewed across all sites.*

Response:

31.2 *If this is a multi-site study where you are the lead investigator, describe the processes to ensure communication among sites, such as the following.*

- *All sites have the most current version of the IRB documents, including the protocol, consent document, and HIPAA authorization.*
- *All required approvals have been obtained at each site (including approval by the site’s IRB of record).*
- *All modifications have been communicated to sites, and approved (including approval by the site’s IRB of record) before the modification is implemented.*
- *All engaged participating sites will safeguard data as required by local information security policies.*
- *All local site investigators conduct the study appropriately in accordance with applicable federal regulations and local laws.*

- *All non-compliance with the study protocol or applicable requirements will be reported in accordance with local policy.*

Response:

31.3 *Describe the method for communicating to engaged participating sites.*

- *Problems (inclusive of reportable events)*
- *Interim results*
- *Study closure*

Response:

31.4 *If this is a multicenter study **where you are a participating site/investigator**, describe the local procedures for maintenance of confidentiality.*

- *Where and how data or specimens will be stored locally?*
- *How long the data or specimens will be stored locally?*
- *Who will have access to the data or specimens locally?*
- *Who is responsible for receipt or transmission of the data or specimens locally?*
- *How data and specimens will be transported locally?*

Response:

31.5 *If this is a multicenter study and subjects will be recruited by methods not under the control of the local site (e.g., call centers, national advertisements) describe those methods. Local recruitment methods are described elsewhere in the protocol.*

- *Describe when, where, and how potential subjects will be recruited.*
- *Describe the methods that will be used to identify potential subjects.*
- *Describe materials that will be used to recruit subjects. (Attach copies of these documents with the application. For advertisements, attach the final copy of printed advertisements. When advertisements are taped for broadcast, attach the final audio/video tape. You may submit the wording of the advertisement prior to taping to preclude re-taping because of inappropriate wording, provided the IRB reviews the final audio/video tape.)*

Response:

32.0 Banking Data or Specimens for Future Use*

- ☒ N/A: This study is not banking data or specimens for future use or research outside the scope of the present protocol. This section does not apply.

32.1 *If data or specimens will be banked (stored) for **future use, that is, use or research outside of the scope of the present protocol**, describe where the data/specimens will be stored, how long they will be stored, how the data/specimens will be accessed, and who will have access to the data/specimens.*

NOTE: Your response here must be consistent with your response at the “What happens if I say yes, I want to be in this research?” Section of the Template Consent Document (HRP-502).

NOTE: If the UBIRB has approved this study to bank data and/or specimens for potential future use outside the scope of this research study, any future use or disclosure of the data that is not described within the approved study must be submitted for review to the UBIRB.

Response:

32.2 *List the data to be stored or associated with each specimen.*

Response:

32.3 *Describe the procedures to release banked data or specimens for future uses, including: the process to request a release, approvals required for release, who can obtain data or specimens, and the data to be provided with specimens.*

Response: