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PROTOCOL TITLE:

Locomotor function following transcutaneous electrical spinal cord stimulation in individuals with chronic hemiplegic stroke

PRINCIPAL INVESTIGATOR:

Elliot J. Roth, MD
Physical Medicine and Rehabilitation
312-238-4864
eroth@sralab.org

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OBJECTIVES:

- To determine whether transcutaneous spinal cord stimulation combined with ambulation training modulates corticospinal locomotor networks in individuals with chronic hemiplegic stroke
- To determine whether transcutaneous spinal stimulation combined with ambulation training improves locomotor function in individuals with chronic hemiplegic stroke
- To determine whether transcutaneous spinal stimulation combined with ambulation training improves symmetry of gait in individuals with chronic hemiplegic
- To determine whether transcutaneous spinal stimulation combined with ambulation training improves standing posture and balance in individuals with chronic hemiplegic stroke
- To determine whether ambulation efficiency (improved cardiovascular conditioning) improves with non-invasive spinal stimulation and locomotor training in individuals with chronic hemiplegic stroke

BACKGROUND:

The use of epidural stimulation has been performed with implanted electrode systems and demonstrated effectiveness in human and animal models after spinal cord injury, but this will be one of the first studies to investigate the efficacy of a painless and non-invasive method of spinal cord stimulation with individuals with hemiplegia due to stroke. This is significant because the transcutaneous epidural stimulation carries less risk (compared to implantation procedure) and more individuals suffer from the consequences of stroke compared to spinal cord injury.

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The use of epidural spinal-cord stimulation was shown to generate locomotion patterning in humans after a complete spinal cord injury¹. The intervention may be effective, but the invasive and involved procedure is not realistic for incorporation into routine rehabilitation services. Recent efforts have induced step-like patterns in patients with a motor complete spinal cord injury using non-invasive spinal cord stimulation. Even more promising is that these individuals were able to demonstrate *voluntary* step-like patterns with continued training.² These results reflect the potential for neuroplasticity modulation through non-invasive spinal stimulation during locomotor training for individuals with a disruption between supra and spinal connections.

We would like to explore the use of this device with patients with a single, chronic stroke history that resulted in hemiplegia. The results of this study will help us understand how transcutaneous electrical stimulation may improve balance and ambulation in individuals with a stroke. The number of people diagnosed with a stroke in the United States is 795,000 per year. Projections estimate that by 2030, there will be an additional 3.4 million adults with a stroke.³ This is a significant number of people that may benefit from this training paradigm.

References:

1. Dimitrijevic MR, Gerasimenko Y, Pinter MM. Evidence for a spinal central pattern generator in humans. Ann NY Acad Sci 1998;860:360-376.
2. Gerasimenko YP, Lu DC, Modaber M, et al. Noninvasive reactivation of motor descending control after paralysis. Journal of Neurotrauma. 2015. 32:1968-1980. Doi:10.1089/neu.2015.4008.
3. Benjamin EJ, Blaha MJ, Chiuve SE, et al. Heart disease and stroke statistics – 2017 update: a report from the american heart association. Circulation. 2017;135:e1-e458. Doi:10.1161/CIR.0000000000000485

INCLUSION AND EXCLUSION CRITERIA:

Inclusion Criteria:

- Participants are 18 years of age or older
- Participants are at least 12 months post stroke
- Participants with hemiplegia secondary to a single stroke
- Functional Ambulation Category of 2 or greater - Patient needs continuous or intermittent support of one person to help with balance and coordination.
- Participants are able to provide informed consent
- Participants are not currently receiving regular physical therapy services

Exclusion Criteria

- Individuals less than 18 years of age
- Individuals with an acute stroke (less than 12 months since stroke)
- Individuals with ataxia
- Individuals with multiple stroke history
- Currently taking medication for spasticity management or depression
- Modified Ashworth score of 3 or greater in lower extremity
- Pregnancy or nursing
- Pacemaker or anti-spasticity implantable pumps
- Active pressure sores
- Unhealed bone fractures
- Peripheral neuropathies

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- Painful musculoskeletal dysfunction due to active injuries or infections
- Severe contractures in the lower extremities
- Cardiopulmonary disease
- Active urinary tract infection
- Clinically significant depression, psychiatric disorders, or ongoing drug abuse
- **TMS Specific Criteria**
 (see **Safety Screening Questionnaire for Transcranial Magnetic Stimulation**)
 - Medicated with agents known to increase (e.g., amphetamines) or decrease motor system excitability (e.g., lorazepam)
 - Implanted cardiac pacemaker
 - Metal implants in the head or face
 - Suffers unexplained, recurring headaches
 - Had a seizure at any time in the past, or has epilepsy
 - Skull abnormalities or fractures
 - Suffered a concussion within the last 6 month
 - Cardiorespiratory or metabolic diseases (e.g. cardiac arrhythmia, uncontrolled hypertension or diabetes, chronic emphysema)
 - Pregnant

STUDY-WIDE NUMBER OF PARTICIPANTS: NA - This is a single-center study

STUDY-WIDE RECRUITMENT METHODS: NA

MULTI-SITE RESEARCH: NA

STUDY TIMELINES:

Participants who meet the study criteria and voluntarily consent are required to attend thirty-two (32) visits in total. This includes:

- One (1) screening/baseline assessment visit
- Twenty-four (24) treatment/intervention visits
 - This is based on an intervention frequency of 3 times per week for 8 weeks
 - Each treatment session may last up to 2 hours
- Two (2) assessment visits that occur after 4 weeks and after 8 weeks of treatment
- Two (2) transcranial magnetic stimulation (TMS) visits that occur before initiation of treatment and after eight (8) weeks of intervention
- Three (3) follow-up visits at 3 months, 6 months and 12 months post intervention
 - Repeat assessment visit measurements

We anticipate an ongoing enrollment over 2 years. Investigators will complete this study (primary analyses) 4 years from start date (IRB approval date).

	Informed Consent	Assessment Visit	TMS	Treatment Visit
Pre-Study	X			
Study Initiation		X	X	
Intervention weeks 1-4				X
Post intervention week 4		X		

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Intervention weeks 5-8				X
Post intervention week 8		X	X	
3 month follow-up		X		
6 month follow-up		X		
12 month follow-up		X		

STUDY ENDPOINTS:

Primary endpoints:

- Improvement in Six Minute Walk Test (6MWT)

Secondary endpoints

- Improvement in Ten Meter Walk Test (10MWT) at self-selected velocity and fastest (safe) velocity
- Improved weight bearing symmetry and reduced center of pressure excursion during static standing with eyes open and eyes closed using a force plate.
- Improved dynamic balance as reflected by an increase in center of pressure excursion without stepping during reaching tasks on a force plate.
- Improved gait kinematics reflected by improved symmetry and decreased base of support during walking on the the GAITRite electronic walkway
- Improved corticospinal excitability as measured from transcranial magnetic stimulation (TMS)

PROCEDURES INVOLVED:

Study Design: A randomized control trial. We are evaluating the effectiveness of transcutaneous spinal cord stimulation on ambulation and standing balance among individuals with hemiplegia due to chronic stroke. We will randomly assign participants into either intervention group A or intervention group B. Intervention group A will receive transcutaneous spinal cord stimulation during the intervention visits while intervention Group B will complete the same interventions without transcutaneous electrical spinal cord stimulation.

STUDY EQUIPMENT

- **Wearable sensors**

The sensors used will include those available from the BioStampRC Discovery Kit (MC10, Inc.) and custom sensors designed by the John Rogers research group at Northwestern University. The wearable sensors will collect the following information:

- Biometric data, including electrocardiography (EKG) and electromyography (EMG)
- Movement data from the limbs including signals from triaxial accelerometers (ACC) and gyroscopes (GYR)
- The rate of sweating and glucose concentration using microfluidic sweat sensor.

Prior to sensor placement, the skin will be prepped and cleaned using alcohol wipes. Sensors are placed on the skin using adhesive stickers that minimize irritation. Medical

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dressings (Tegaderm, 3M) may also be used to ensure adhesion and proper contact with the skin. Sensors will be cleaned with soap and water before and after use. The battery life of each sensor will depend on which signal modalities are activated for that sensor (e.g. ACC only: 8-35 hours, ACC+GYR: 2-4 hours, ACC+EMG: 11 hours).

- **Electronic walkway**

The GAITRite electronic walkway contains sensor pads encapsulated in a carpet and connected to a computer. The system can be laid over any flat surface and automates measuring temporal and spatial gait parameters. The GAITRite electronic walkway for the study shall be a minimum of 14 feet long. The GAITRite data capture was chosen as measurement of the patient's overall gait quality. Patients will be asked to walk at a self-selected speed and a fast, but safe, speed across the GAITRite electronic walkway.

- **Force platform sensor**

The AMTI Force System from Water Town, MA will be used to assess balance. The platform is placed on the floor and subjects stand on the device. The force plate measures the forces and movements applied to its top surface as a patient performs static and dynamic balance activities, which are outlined below in the assessment section.

- **Gravity Eliminated locomotion training**

A custom designed apparatus to allow the lower legs to move in a gravity neutral position. Participants are positioned in a side-lying position on their non-paretic side. Their legs extend off the edge of the mat table. The upper leg is supported at the shank and the lower leg is placed on a rotating brace attached to a horizontal board supported by vertical ropes secured to the ceiling. In this gravity-neutral position, the participants will be requested to perform rhythmic stepping-like motions. Both interlimb and intralimb coordination will be quantified based on the limb kinematics and EMG of selected flexor and extensor leg muscles with and without the use of transcutaneous spinal stimulation.

- **Transcutaneous Spinal Cord Neurostimulator (NeuroEnabling Stimulator System)**

The Transcutaneous Spinal Cord Neurostimulator manufactured by NeuroRecovery Technologies, Inc. will deliver transcutaneous electrical spinal cord stimulation. It provides constant current stimulation with a range of 0-250 mA through self-adhesive electrodes (ValuTrove, Axelgaard Ltd., USA) with a diameter of 3.2 cm placed as cathodes on the skin between the spinous processes of the C4 and Co1 vertebrae. In addition, two 7.5 × 13 cm self-adhesive electrodes serving as anodes (ValuTrove, Axelgaard Ltd., USA) will be placed symmetrically on the skin over the iliac crests. A foam rubber pad will be placed over the cathodes and secured using adhesive tape, and an elastic belt will be wrapped tightly around the trunk above the waist to ensure a constant pressure between the electrodes and the skin. The stimulation waveform will consist of monophasic, rectangular 1-ms pulses at a frequency ranged between 0.2 and 40 Hz, with each pulse filled with a carrier frequency of 5 to 10 kHz. The stimulation intensity will vary from 10 to 150 mA and be determined based on participant threshold and maximum motor outputs.

- Three stimulating electrodes are placed at the interspinous spaces between C5 and C6, T11 and T12, and L1 and L2 vertebrae. The number of stimulating channels will be adjusted individually and depends on activity and functional outcome at 4-6 bilateral lower limb muscles: Vastus lateralis (VL), rectus femoris (RF), medial hamstring (MH), tibialis anterior (TA), medial gastrocnemius (MG), and soleus (SOL).

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- Peripheral Nerve Stimulation: Calf muscles stimulation may be provided via the tibial posterior or common peroneal nerves using surface electrodes at an intensity range from 0 to 100 mA with a frequency of 0.2 to 40 Hz applied.

- **Cosmed K4B² Metabolic unit**

Cosmed K4B² (K4B2 Cosmed, Italy) is a portable gas analysis system that measures oxygen consumption (VO₂) and Carbon-dioxide production (VCO₂) in a breath by breath fashion. K4B² system consists of a portable unit and battery pack that weight about 2.4 lbs (1100 gm). The portable unit has O₂ and CO₂ analyzers that are bi-directionally connected to a flowmeter and turbine attached to a rubber facemask that is tightly strapped over subject's nose and mouth. K4B² requires calibration before every testing session due to usage of heated sensors for measurements. Manufacturer's recommend at least 45 minutes warm up time for unit under ambient temperature (ideally at 20°C) before calibration. K4B² calibration involves verifying flowmeter and concentrations of gases with labeled concentrations. K4B² acquires heart rate using a telemetric heart rate sensor that is strapped over subject's thorax. The K4B² and battery pack can be securely placed in slots on a standard harness worn by subject. This harness allows access to buttons on the unit on upper back and minimal interference to activities like walking. Data extraction and processing is carried using K4B² custom software.

- **Transcranial Magnetic Stimulation (TMS)**

TMS is a safe, non-invasive, painless method of brain stimulation that has been widely used to study the physiology of the representations of muscles in the motor cortex in healthy and neurologically disordered individuals. Very short duration (< 1 ms) magnetic pulses are applied via an insulated wire coil placed on the intact scalp overlaying the motor cortical area projecting to a target muscle. Each pulse induces a motor evoked potential (MEP) in a target muscle that can be readily monitored by recording Electromyogram EMG from that muscle. In this study, TMS is being used to assess changes in corticospinal excitability that may occur following repeated transcutaneous spinal stimulation and ambulation training. A figure-of-eight or double cone coil is typically used to deliver focal magnetic pulses to a number of scalp sites over the cortical area representing a muscle of interest. Self-adhesive disposable electrodes (Delsys) with an inter-electrode distance of 2 cm will be applied over the muscle bellies of the quadriceps, hamstrings, ankle dorsiflexors and ankle plantarflexors in the lower extremity. A ground electrode will be applied over the patella. Standard skin preparation techniques (light abrasion and cleansing with alcohol) will be completed prior to application of the electrodes. EMG recordings will be amplified (Delsys, Bagnoli EMG), band-pass filtered (10-1000 Hz), and sampled at 5000 Hz. Electromyographic (EMG) activity will be collected from the all the muscles bilaterally. Magnetic stimuli will be delivered via a double cone coil/figure of eight connected to a Magstim 200 unit (Magstim Company, Boston MA). The resting and active threshold for TMS will be determined for each subject. TMS measurements will involve generating motor evoked potentials (MEP) for each muscle from two different coil positions – 2cm on either side of the vertex. Motor evoked potentials (MEPs) at intensities ranging from 70 – 140% active threshold will be generated for each muscle from each coil position. A figure-of-eight or double cone coil will be used to deliver focal magnetic pulses. Resting motor threshold for the muscle of interest in will be defined as the stimulator output intensity that can elicit motor evoked potentials (MEPs) with peak-to-peak amplitude more than 50 µV in four out of eight trials. It will be determined by increasing stimulus intensity in steps of 1% stimulator output. Active thresholds will be determined with the same protocol, however with the subject contracting the muscle of interest to about 10% of maximum voluntary contraction. Subjects will receive approximately

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100 – 150 pulses of stimulation. These measures will assist the investigator and coinvestigators in generating recruitment curves, which will help assess the corticospinal excitability of the ipsilateral and contralateral motor cortex to each lower limb muscle.

VISIT SCHEDULE & DESCRIPTION

Visit 1: Initial screening session

- Obtain voluntary and informed consent
- Inclusion/exclusion criteria checklist reviewed with patient, including the TMS screening form
- Medical history review
 - Patient name
 - Patient date of birth
 - Patient race (voluntary)
 - Patient gender
 - Date of stroke
 - Type and location of stroke
 - Paretic/non-paretic limb
 - Assistive device use
 - Recent surgery/injuries
 - Allergies
 - Therapy history
- Patient Health Questionnaire – 9 (PHQ-9) completed by patient for depression detection
- Standard evaluation of physical function
 - Active and passive range of motion of bilateral lower extremities
 - Muscle strength screen using manual muscle testing of lower extremities
 - Assessment of lower extremity spasticity using Modified Ashworth Scale
 - Assessment of gait for ataxia and level of independence with Functional Ambulation Category
 - Skin integrity screen
- Functional outcome measurements
 - Six Minute Walk Test (6 MWT)
Participants will complete with wearable sensors and Cosmed K4B² Metabolic unit to determine participant's baseline gait efficiency
 - Ten Meter Walk Test (10 MWT)
Participants will complete at their self-selected speed (SSV) with wearable sensors and CosmedK4B² Metabolic Unit to determine baseline gait speed and community ambulation assessment
- Locomotion assessment for inter and intra limb coordination using wearable sensors (described above) under the follow conditions:
 - Overground locomotion

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Participants will ambulate along Gait Rite electronic walkway 6 times (3 times per gait speed) to evaluate baseline gait pattern at both their self-selected and safe fast gait speed.

- **Standing balance**

Two different aspects of balance will be evaluated during standing: static and dynamic stability. During the static stability test, the participants will be instructed to stand on the force plate as still as possible for 60 seconds with their eyes open. After 2 minutes of rest, the task will be repeated with the eyes closed. The excursions of the center of pressure (COP) and EMG of leg muscles will be analyzed.

During the dynamic stability test, the ability to voluntarily displace the COP to a maximum distance without losing balance will be assessed (Limits of stability (LOS) test). The participant will be instructed to lean forward, backward, left, and right, hold the position for ~5 seconds and return back to the initial/center position.

Transcranial Magnetic Stimulation (TMS) Visits

Each participant will complete two (2) TMS visits. The first TMS session will occur before initiation of treatment/intervention. The second TMS visit will occur after the 24 treatment visits are completed.

Treatment Sessions

Each participant will complete 24 treatment sessions over the course of 8 weeks. Each treatment session will include:

1. Thirty minutes of gravity-eliminated locomotion training performed in side-lying position using the harness system for leg support with and without transcutaneous spinal stimulation.
 - a. Intervention group A
 - i. 30 minutes with the transcutaneous electrical spinal cord stimulator.
 - b. Intervention group B
 - i. Up to 30 minutes without the transcutaneous electrical spinal cord stimulator
2. Thirty minutes of progressive treadmill training with and without the use of transcutaneous spinal stimulation.
 - a. Intervention group A
 - i. 30 minutes with the transcutaneous electrical spinal cord stimulator
 - b. Intervention group B
 - i. 30 minutes without the transcutaneous electrical spinal cord stimulator

Under both of the conditions, the goal is to generate smooth and symmetrical stepping movements. The trained research personnel will provide cues (verbal, visual and tactile) to improve symmetry of gait and avoid compensatory mechanisms. The progression in training refers to gradually increasing gait speed while maintaining improved gait kinematics.

Functional Assessment Visits

Two visits that occur after 4 weeks and after 8 weeks of treatment

- Refer to initial screening visit for repeat of assessments
- In addition, participants will complete a second assessment of the 10 MWT and the electronic walkway (GAITRite) as described above while receiving transcutaneous

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electrical spinal stimulation. This will assist with determining any immediate changes with and without the use of the device during over-ground ambulation.

Follow-up Assessment Visits

Three visits that occur after the last treatment visit at the following increments: 3 months post intervention, 6 months post intervention, and 12 months post intervention

- Refer to functional assessment visits for repeat of assessments
 - As indicated above, all subjects will repeat the 10 MWT and electronic walkway (GAITRite) assessments with the use of transcutaneous electrical spinal cord stimulation. This will assist with determining immediate changes with and without the use of the device during over-ground ambulation.

SAFETY MONITORING

All visits will be under the supervision of a trained researcher and clinician. Manual assistance or cueing will be provided as necessary for safety and balance. Clinicians will also utilize gait belts and overhead harness systems to ensure patient safety during physical activity. Vital signs will be monitored with use of our wearable sensors before, during and after physical exertion. All subjects will be permitted to stop physical activity or rest at any time during the study. In addition, the following patient reports will be used to assess patient participation and make adjustments as appropriate.

- **Rating of Perceived Exertion (RPE)**

The 15-grade Borg Scale during ambulation training (overground, treadmill and gravity-eliminated) to monitor RPE. The intensity will be adjusted to ensure patients do not exceed a rating of 17 (very hard).

- **Pain scale**

Visual Analogue Scale (VAS) for pain will monitor patient discomfort during non-invasive spinal cord stimulation and locomotion training parameters. This is a 10-point scale. We will stop when the participant states pain that interferes with their safe participation in the research.

DATA AND SPECIMEN BANKING:

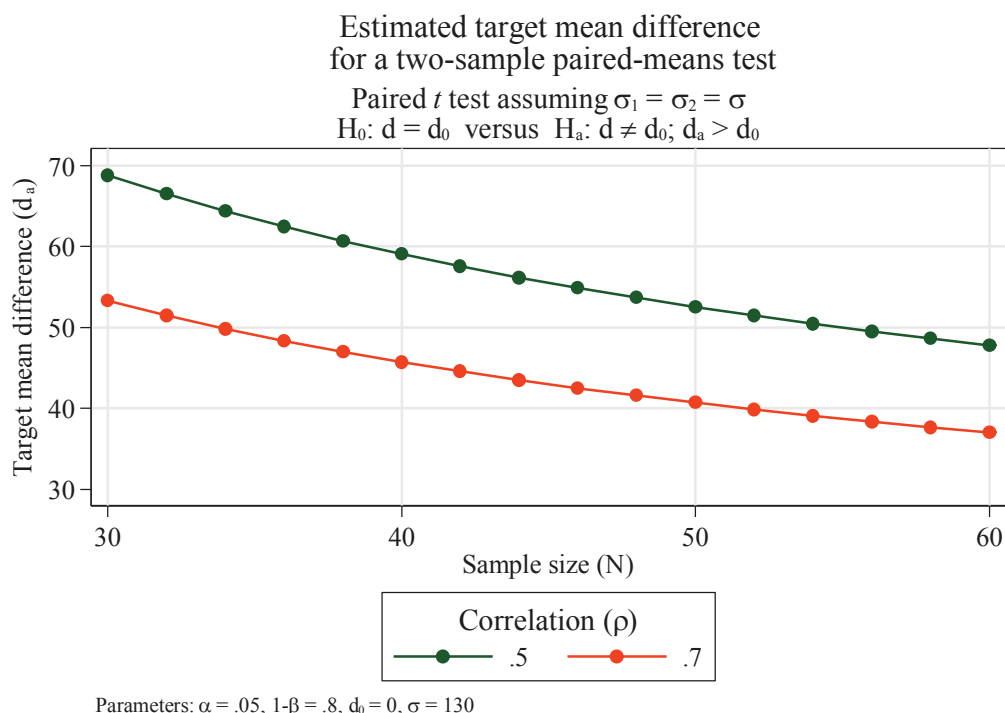
Data will be collected and kept confidential and compliant with HIPAA requirements. All personal information and study documentation that can identify participants will be kept secure to protect their privacy and will never be shared at any time with any person or entity. Data collected during the study and shared with others will reference participants only by an alphanumeric code. The “master list” linking personal information to the alphanumeric code will not be shared. All data will be captured in electronic format and stored on the secure and password protected network and devices managed by the Shirley Ryan AbilityLab. Electronic folders will be private with limited access as determined by the PI.

DATA AND SPECIMEN MANAGEMENT:

Sample Size and Power Considerations. The primary endpoint in this single-arm study will be the change in distance walked during the 6 minute walk test (6MWT) from baseline to the 4-week post-treatment follow up evaluation. The minimal clinically important difference (MCID) for the 6MWT is MCID=50m, and we base our sample size determination based on the ability to detect such a difference. Paz et al report a study conducted in n=30 patients with chronic hemiplegia/hemiparesis with ≥6 months since stroke. At their baseline evaluation the mean (SD) distance walked on the 6MWT was 270.67+/-129.18m, and speed was 0.75 +/- 0.36 m/s. Assuming similar variability in our patient population, a sample size of n=34 will provide 80% power with alpha=0.05 to detect an improvement from 270m to 319.85m (i.e. $\Delta = 49.85\text{m}$) when

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the within-subject correlation between pre- and post-treatment measures is $\rho = 0.7$, based on a paired t-test. A larger sample size of $n=56$ would be necessary to detect $\Delta = 49.5m$ if the within-subject correlation between pre- and post-treatment measures is $\rho = 0.5$.



Statistical Analysis Plan. The primary endpoint of this study is the improvement in 6MWT distance following therapy. The primary analysis will be conducted using a paired t-test. Paired t-tests will be similarly used to investigate changes in other outcome measures from baseline to the 4-week follow-up. Because functional outcomes will be assessed at two follow-up visits, we will use a linear mixed model with repeated measures to jointly assess changes at 4 and 8 weeks post-treatment relative to baseline. These models will include as fixed effects the evaluation time point (baseline, 4 and 8 week f/u as a categorical variable), treatment intensity (e.g. total number of sessions completed), time since stroke onset and other relevant baseline clinical factors. This model will also allow us to appropriately model the within-subject correlation between repeated measurements (e.g. using an autoregressive variance-covariance structure). In addition, linear mixed models provide a better mechanism for handling missing data by using all available data, rather than performing a complete case analysis, if the data are assumed to be missing at random.

PROVISIONS TO MONITOR THE DATA TO ENSURE THE SAFETY OF PARTICIPANTS:

NA. This study does not involve more than Minimal Risk to participants.

WITHDRAWAL OF PARTICIPANTS:

Participants may be withdrawn from the study without their consent by the PI if there are any safety concerns for continued participation. This may be due to a change in medical status at any point during the study. Participants may withdraw from the research voluntarily at any time.

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The research team may request reason for their withdrawal to monitor study participant attrition. Data collected until point of withdrawal will be maintained.

RISKS TO PARTICIPANTS:

There is a minimal risk of skin irritation from electrodes or wearable sensors and the adhesive materials used to secure them to the skin. Participants will be screened for adhesive allergies or previous reaction. If a subject has a known allergy to sensor and/or electrode adhesive, an alternate method will be explored. If the patient is unsure of a skin sensitivity, a small test patch will be applied at screening session. Trained research personnel will perform frequent skin check to all wearable sensors and electrodes.

Participants may experience an increase in respiration, shortness of breath, increased heart rate, lowering or elevation of blood pressure and/or dizziness. Most subjects will experience an increase in respiration and heart rate due to increased activity. We do not expect the increase in respiration and heart rate to be greater than what is normally experienced in an individual during regular exercise. This discomfort is reversible and all subjects will be permitted to stop physical activity or rest at any time during the study. Clinicians will use patient report (pain scale, BORG), cardiovascular monitoring devices (EKG, HR) and clinical judgment to monitor signs and symptoms throughout intervention. Intervention will stop immediately and standard medical procedure will follow any rare event of prolonged or worsening discomfort.

There is some chance that participants may sustain muscle and joint soreness due to the potential increase in activity. To minimize this risk, researchers will monitor the participant for verbal and visual signs of fatigue and/or discomfort and will be offered adequate rest periods.

There is also a risk of a thermal reaction (a burn) to the skin and surrounding tissue from the transcutaneous electrical stimulation. To prevent a burn from occurring there is a built-in safety cut-off switch in the device to prevent delivering energy levels (electricity) beyond acceptable limits. There are also safety features in the software program that controls the device to limit the amount of time you are exposed to the stimulation

The risk of bruising from the gravity supporting harness equipment. This risk will be minimized by a thorough skin check by experienced research personnel. Adjustments to the device fit, placement and additional padding will be assessed to decrease the risk of skin breakdown.

There is a risk of falling during ambulation and balance activities. This risk will be minimized by having an experienced research personnel conduct the participant sessions with verbal cues, manual assistance, overhead attachment with a safety harness and/or gait belt.

There is a low risk of seizure associated with TMS. Some stroke patients experience post stroke seizures which might elevate the risk of TMS should they be included in a study, however, our screening procedure eliminates these individuals. A majority of the TMS studies conducted at the Neuralplasticity Lab of the SRALab over the last 9 years have included both healthy individuals and post stroke patients (including a current clinical trial with sub-acute stroke and rTMS) and no reportable adverse events have occurred during single pulse TMS (such as in the present protocol), paired-pulse TMS, or down-regulatory repetitive TMS interventions protocols. The stimulation parameters in the present protocol are well within published safety guidelines for this population (Rossi et al 2009). All individuals will be carefully screened for the following contraindications to TMS (as listed in the protocol, consent form, and separate TMS safety

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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. Individuals with any such contraindications will be excluded from the study. Therefor those individuals included will only be those to which TMS can be safely applied.

POTENTIAL BENEFITS TO PARTICIPANTS:

There may be no direct benefit to the participants. The main benefit of participation in this study may help us have a better understanding of transcutaneous spinal stimulation procedures and may help other people through future development of these devices and procedures.

VULNERABLE POPULATIONS: NA

COMMUNITY-BASED PARTICIPATORY RESEARCH: NA

SHARING OF RESULTS WITH PARTICIPANTS:

There is no intent to share information with participants. However, if a patient requests information about their individual results, the results of their outcome measures will be shared verbally. No results of other study participants will be shared to maintain patient confidentiality.

SETTING:

All research and procedures will be conducted at the Shirley Ryan AbilityLab, 355 E. Erie Street, Chicago, IL. Study data and results may be shared with our research collaborators at the Edgerton Neuromuscular Research Laboratory at the University of California, Los Angeles, CA. Any data shared will be de-identified to ensure patient privacy.

RESOURCES AVAILABLE:

The Shirley Ryan AbilityLab services the stroke population at a rate of approximately 300 new patients per year. The Shirley Ryan AbilityLab is a research hospital that maintains a research registry (greater than 750 participants). In addition to our flagship hospital, we have outpatient clinics that provide long-term follow-up care to this population. We will recruit participants from our research registry, website and outpatient affiliates and facilities to meet our enrollment goal.

All study team members will be trained on the study protocol and procedures. Experienced physical therapists will lead the assessment and treatment sessions. The study team members are employees of the Shirley Ryan AbilityLab. They are familiar with the study site and are experienced with the study population. There will be medical resources including a resident on call and nursing staff available 24 hours a day if needed in case of an emergency. All our treadmills have overhead harnesses for additional safety during training.

PRIOR APPROVALS: NA

RECRUITMENT METHODS:

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The Shirley Ryan AbilityLab maintains a research registry of individuals that have voluntarily opted to receive notification of research studies. We would initiate a Research Data Request to compile a list of individuals that requested study notification and have a medical history significant for stroke. We will contact those individuals captured in our Research Data Request.

In addition, we would update our website (www.sralab.org) to include this research project under current clinical trials and studies.

We created flyers to distribute to off-site Shirley Ryan AbilityLab facilities and stroke support groups. We will email flyers to Shirley Ryan AbilityLab physician clinics for clinicians to provide to patients.

NUMBER OF LOCAL PARTICIPANTS:

This is a single-center study with an enrollment goal of 45 participants, with a 20% drop out rate we hope to complete 36 participants. Participants will be randomized into an intervention group with the goal for 18 completed subjects in each arm.

CONFIDENTIALITY: NA

PROVISIONS TO PROTECT THE PRIVACY INTERESTS OF PARTICIPANTS:

All personal information (names, addresses, email or phone numbers, etc.) gathered for this study that can identify participants will be kept secure to protect their privacy and will not be shared with any person or entity. Data collected during the study and shared with others will reference participants only by an alphanumeric code. The “master list” linking personal information to the alphanumeric code will not be shared, and will be kept by the study PI in a secure location.

Every possible precaution will be taken to protect the privacy interests of subjects. To begin with participation in the study is completely voluntary. Trained research personnel will explain the purpose of the study and intended use of subject’s personal health information and precautions taken to keep the study information and data confidential. The research team does not have access to previous medical records. All information gathered for study purposes will be completed at the screening visit.

COMPENSATION FOR RESEARCH-RELATED INJURY:

If the subject gets an injury or illness as a result of study, the subject is required to promptly notify the PI of the study about the illness or injury. The Shirley Ryan AbilityLab will not pay for medical care required because of a bad outcome resulting from participation in this research study. However, this does not keep subject from seeking to be paid back for care required because of a bad outcome.

ECONOMIC BURDEN TO PARTICIPANTS:

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Participants are responsible for transportation to/from Shirley Ryan AbilityLab. Participants are responsible for any parking costs. Participants are required to attend all 32 visits. Each visit may last up to 2 hours. Participants will receive \$25 per visit to help ease the burden of transportation.

CONSENT PROCESS:

The consent process will occur at the Shirley Ryan AbilityLab. The consent form will be reviewed at the initial screening visit. If consent is granted, the participant will complete the rest of the screening visit assessments (as outlined above). If the patient decides to consent at a later date, the screening visit assessments will be scheduled for a later time, when the participant is willing to participate. Participation is strictly voluntary and subjects may withdrawal from study at any time. The consent discussion will take as long as necessary for patients to make an informed and voluntary consent. The consent and research personnel will thoroughly review the consent form. The language used during discussion and contained in the consent form will be provided in non-medical language to ensure participants fully understand the study.

(For Non-English Speaking Participants) NA

Waiver or Alteration of Consent Process: NA

PROCESS TO DOCUMENT CONSENT IN WRITING:

Participants will review a hard copy of the consent form with an authorized research team member. The participants will be provided a copy of their signed consent form. The screening researcher or clinician will verbally review the forms and be available for any questions. The signed documents will be scanned and saved on the Shirley Ryan AbilityLab's secure network in a private folder.

DRUGS OR DEVICES:

All research devices will remain at the Shirley Ryan AbilityLab in a secure research location. Only authorized research personnel will have access to the devices.