Transcutaneous Stimulation to Enhance Walking after Spinal Cord Injury

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1. Title: Transcutaneous spinal direct current stimulation to enhance locomotion after spinal cord injury

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3. Abstract:

Locomotor training is a well-established rehabilitation strategy that promotes walking recovery after ISCI.[1-4] A primary objective of this approach is to promote recovery of spinal locomotor circuitry through excitation from descending motor signals and afferent somatosensory inputs to the spinal cord.[5,6] Following locomotor training, individuals with ISCI often demonstrate improved walking function.[1,3,7,8] However, most people with ISCI continue to have serious walking impairments that limit mobility, community participation and quality of life.[2,7,9] A key limitation of current rehabilitation approaches, including locomotor training, is insufficient excitation of spinal locomotor circuitries.[6,10,11] Excitation is needed to drive neuroplastic recovery. Since the majority of SCIs are incomplete, a promising strategy to promote spinal excitation is to use adjuvant approaches that leverage spared pathways and the intact afferent pathways below the level of the lesion.[5,12,13] Transcutaneous spinal direct current stimulation (tsDCS) is a neuromodulatory approach that uses mild and non-invasive electrical stimulation.[14,15] tsDCS induces immediate and lasting changes in spinal cord excitability[14,16-18] and alters reflexive and voluntary behaviors in rodents.[19] Likewise, in humans, tsDCS modulates spinal reflexes,[20] increases corticospinal excitability,[21] and increases motor unit recruitment.[22] Although ample mechanistic evidence suggests that tsDCS could substantially enhance the therapeutic effect of locomotor rehabilitation, this combinatorial approach has not been evaluated in humans with SCI. We propose a proof-of-concept study to investigate the effects of tsDCS on locomotor function and rehabilitation outcomes in individuals with ISCI. The immediate effects of tsDCS will be examined by testing changes in muscle activation, walking kinematics and spinal reflex excitability after a single period of tsDCS application. Furthermore, we will test the hypothesis that tsDCS applied during a regimen of locomotor training will improve the functional walking

outcomes achieved. Results of this pilot project may contribute to the development of a combinatorial rehabilitation strategy that leverages current best practice and a novel non-invasive neuromodulation approach to enhance recovery of walking after ISCI.

4. Background:

Locomotor training is a well-established rehabilitation strategy that promotes walking recovery after ISCI.[1-3,7-9,23-27] Locomotor training emphasizes repetitive and task-specific practice of coordinated walking, often with therapist assistance or cueing to promote high quality movement patterns. A primary objective of this therapy is to promote neuroplastic recovery of spinal locomotor circuitry through excitation from descending motor signals and afferent somatosensory inputs to the spinal cord.[5,28] Somatosensory inputs include limb loading and hip extension, which are known to elicit afferent volleys that are important for facilitating propulsion and swing initiation, respectively.[29-34] Following locomotor training, individuals with ISCI often demonstrate improved walking function.[1-3,7-9,23-27] However, most people with ISCI continue to have serious walking impairments that limit mobility, community participation and quality of life.[1-3,7,9] Adjuvants that increase spinal excitation during locomotor training may enhance the effectiveness of this therapy.[6,35]

A key limitation of current rehabilitation approaches is insufficient excitation of spinal locomotor circuitries.[6] Excitation is necessary to drive Hebbian learning and activity-dependent neuroplasticity. Since the majority of spinal cord injuries are incomplete, a promising strategy for promoting excitation of the spinal cord is to use adjuvant/combinatorial approaches that leverage spared pathways and the intact afferent pathways below the level of the lesion.[13,28,35] Here we propose to combine transcutaneous spinal direct current stimulation (tsDCS) with locomotor training to increase spinal excitation and thereby increase the effectiveness of locomotor rehabilitation. tsDCS is a neuromodulation approach that uses a mild electrical current to alter the membrane potential of spinal neurons.[18,36] We propose to use an electrode montage that has been shown to induce a net depolarization, thereby bringing neurons closer to their discharge threshold.[21,22] When applied during walking, this increased excitability of spinal neurons contributes to a physiological environment that is more responsive to task-specific activation by descending/motor and afferent/somatosensory pathways.[37] This combinatorial strategy is particularly promising because tsDCS is a relatively simple, non-invasive approach that realistically could be implemented in clinical settings. Overall, accumulating evidence indicates that a combined tsDCS strategy is likely to be effective and is a critical next step in advancing neuromodulation for locomotor rehabilitation.

tsDCS modulates spinal reflexes and locomotor circuits. tsDCS involves the delivery of a mild constant direct current over the spinal cord through surface electrodes. This approach is noninvasive, relatively simple and well tolerated. tsDCS can induce immediate and lasting changes in spinal cord excitability[16,38,39] and can alter reflexive and voluntary behaviors in rodents.[19] During locomotion, tsDCS has been shown to modulate both alpha and gamma motor neuron activity and improve rhythmic motor output.[19] Specifically, tsDCS has been reported to modulate somatosensory input and improve the coordination and amplitude of muscle activation during treadmill locomotion.[19] Human

data indicate that tsDCS increases corticospinal excitability[21] and motor unit recruitment.[22]

tsDCS also modulates spinal reflexes in humans[18,36,40,41] which may be beneficial for improving walking function after ISCI.[15] After ISCI, spinal reflexes are altered and poor reflex modulation contributes to walking impairments.[42,43] For instance, reflex hyper-excitability and reduced post-activation depression of the Hoffman reflex (H-reflex) contributes to over-activation of the ankle plantarflexors during walking.[44-46] tsDCS has been shown to increase post-activation depression in heathy individuals,[47] suggesting tsDCS could have a beneficial effect on walking function in adults post SCI. These effects may be even greater when combined with walking rehabilitation since walking rehabilitation is also known to modulate spinal reflexes by increasing post-activation depression[48,49] and improving reflex modulation during walking.[6,46,50]

Overall, studies of tsDCS support its use as a neuromodulatory approach. The next important step is to test whether this approach can substantially augment the effectiveness of locomotor rehabilitation and improve the neuromuscular control of walking in individuals with ISCI and other neurological conditions.[51] Also noteworthy is that the potential efficacy of tsDCS is supported by a parallel body of evidence from direct current brain stimulation, which shows gains in motor and cognitive function for neurologically-impaired populations such as adults post-stroke.[51-54]

5. Specific Aims:

Specific Aim 1 (Cross-sectional): To test the hypothesis that tsDCS applied during walking will improve muscle activation and lower limb kinematics in adults with chronic ISCI. A random order, double blind cross-over study will be conducted across two test sessions to compare the immediate effects of two dosages of tsDCS during walking. The higher dosage of tsDCS aligns with previous research protocols, while the lower dosage can be effectively be viewed as sham stimulation. Bilateral lower extremity surface electromyograms and 3-dimensional kinematics will be recorded. Outcomes will be changes in muscle activation amplitude and timing, and hip joint excursion during walking. tsDCS induced changes in spinal excitability, as measured by tests of the Hoffman reflex (H-reflex), also will be assessed.

Specific Aim 2 (Interventional): To test the hypothesis that tsDCS applied during 16 sessions of locomotor training will improve functional walking outcomes. Participants will be randomized to receive 16 sessions of tsDCS at one of the two dosages with locomotor training. Primary functional outcomes will include standardized clinical tests of walking speed and endurance. Secondary outcomes will include quantifying changes in muscle activation amplitude and timing, lower limb kinematics and the cortical control of walking during over ground walking.

6. Research Plan:

Recruitment

A minimum of eight individuals are required to complete this pilot study. We aim to screen 30 individuals and enroll 20 subjects in this study. The target population will be

individuals with SCI. Study procedures will take place at Brooks Rehabilitation, which includes a clinical research facility directed by Dr. Emily Fox (Principal Investigator). Potential participants will learn about the study and be recruited in the following primary ways:

1. *Local advertisements or study flyers* (see Recruitment Methods attachments for study flyer and email script for potential participants). Individuals may contact study personnel at Brooks Rehabilitation. Study staff will be available to answer any questions and if the potential participant is interested, the individual will be screened for eligibility (screening process detailed below).
2. *Health care providers at Brooks Rehabilitation or other clinics in the north Florida area (e.g. physicians, physical therapists, or occupational therapists)* (see Recruitment Methods attachments for email script for healthcare providers). Health care providers may ask potential participants if they would like to learn more about a current research study. If interested, the potential participants will be provided with a flyer, which will contain instructions for contacting the study staff at the Brooks Rehabilitation Motion Analysis Center. Study staff will be available to answer any questions and if the potential participant is interested, the individual will be screened for eligibility.
3. *Additionally, the health care provider may ask the potential participant if they are interested in being contacted by a study staff member regarding this research study* (see Recruitment Methods attachments for authorization to release patient information form). If written authorization is provided by the potential participant, the health care provider will request his/her name, telephone number, and email address in order to be contacted by the study staff directly. This recruitment strategy will be necessary to help facilitate communication between the potential participant and the study staff. Study staff will contact the potential participant and answer any questions. If the potential participant is interested, the individual will be screened for eligibility.
4. *Individuals admitted to Brooks Health System.* All individuals admitted to Brooks Health System sign a Brooks Notice of Privacy Practices upon admission which indicates their information may be used for research (see Recruitment Methods section attachments for Brooks Notice of Privacy Practices). This is a standard practice for the Brooks Health System facilities. We have attached this form to the Recruitment Methods section. For individuals who sign this form, Brooks Research Recruitment personnel have permission to access their medical records for research-related purposes. Therefore, Brooks Research Recruitment personnel would be aware of our study (as it is being conducted at a Brooks facility) and would include this as one of several potential research study opportunities when contacting Brooks patients. This procedure is independent of our research study procedures and is carried out by Brooks Research Recruitment personnel; potential participants will only be contacted for screening for this specific study if they indicate to Brooks Research Recruitment personnel that they want to learn more about our study.

Screening and Enrollment

Individuals who are interested in participating in the study will be asked to complete a three-step screening process to determine if they are eligible to participate. **Informed consent will be obtained twice**- once during screening and, if enrolled for the full study, a second time for the study procedures. Individuals will have ample opportunities to ask questions about the study prior to enrollment.

The screening procedures will verify the participant meets the following inclusion and exclusion criteria:

Inclusion criteria

1) Male or female, ages 18-65
2) Single spinal cord injury (duration >1 year) classified as neurologic level T12 or above based on the International Standards for the Neurologic Classification of Spinal Cord Injury, and classified on the American Spinal Cord Injury Association (ASIA) Impairment Scale (AIS) as 'C' or 'D' motor incomplete
3) Capable of ambulating 10 feet with or without the use of gait devices, braces, or the assistance of one person
4) Medically stable with no acute illness or infection
5) Able to provide informed consent

Exclusion criteria

1) Current diagnosis of an additional neurologic condition such as multiple sclerosis, Parkinson's disease, stroke, or brain injury
2) Presence of unstable or uncontrolled medical conditions such as cardiovascular disease, myocardial infarction (<1 year), pulmonary infection or illness, renal disease, autonomic dysreflexia, infections, pain, heterotopic ossification
3) Cognitive or communication impairments limiting communication with study staff or ability to provide informed consent
4) Lower extremity joint contractures limiting the ability to stand upright and practice walking
5) Skin lesions or wounds affecting participation in walking rehabilitation
6) Acute or unstable fracture, diagnosis of osteoarthritis or bone impairments affecting safe participation in walking rehabilitation
7) Severe spasticity or uncontrolled movements limiting participation in walking rehabilitation
8) Body weight or height that is incompatible with safe use of a support harness and body weight support system
9) Pain that limits walking or participation in walking rehabilitation
10) Current participation in rehabilitation to address walking function
11) Botox injections in lower extremity muscles affecting walking function within 4 months of study enrollment
12) Legal blindness or severe visual impairment
13) Known pregnancy
14) Implanted metal hardware of the spine below the 8^{th} thoracic vertebrae

At the discretion of the Principal Investigator, any individual may be deemed ineligible for further participation in this study if there are concerns about the individual's capability to perform study procedures or if it may be unsafe for the volunteer to participate in the study. Furthermore, minor exceptions to the inclusion/exclusion criteria may be permitted at the discretion of the Principal Investigator if those exceptions do not influence participant safety. For example, a small deviation from the requirement for the participant to walking 10 feet with minimal assistance (i.e. able to walk 8 feet) may be permitted if they demonstrate the capacity to complete the testing and training. This is important to ensure that individuals are not excluded for insignificant reasons and to facilitate meeting enrollment benchmarks.

Step one- phone screening

Once a potential participant makes contact with study staff through one of the above-mentioned means, an IRB-approved phone script and screening form will be used to guide the phone screening process (see Recruitment Attachments for phone screening script). Depending on preference, we can also conduct this screening in person. The screening form, designed to avoid collection of protected health information, will ask subjects general information about their eligibility. This information may include health status, physical functioning, history of neurologic impairments, the date of their SCI, movement and sensory impairments, other secondary medical conditions and other information pertaining to inclusion/exclusion criteria. If any potential participant is deemed ineligible for the study during this or a later step of the screening process, all study documentation that had been collected regarding the individual will be destroyed. If an individual passes step one of the screening process and would like to continue with the screening process, participants will be informed of the on-site screening (step two) and medical screening (step three) processes.

Step two- on-site screening

Participants will be asked to come to Brooks Rehabilitation for the on-site screening. At the beginning of this visit, informed consent will be obtained, using the ICF-Screening form for guidance, to inform the individual of the purpose, procedures, possible benefits/risks, alternative to the screening process, and how the individual's protected health information will be collected, used, and shared with others. The potential participant will have the opportunity to review the ICF-Screening and a study staff member will be available to answer questions. We anticipate that some potential participants may want to meet with study staff ahead of time to discuss the screening and study procedures. If so, the informed consent process for the screening may occur on a separate day based on the preference of the potential participant.

The screening will involve clinical tests of motor function (i.e. clinical tests of strength) and functional mobility tasks such as standing and walking. The potential participant will be asked about any conditions of pain and we will confirm any details pertaining to their health and functioning to verify their ability to perform locomotor training (condition of skin, range of motion, spasticity). The following tests, or portions of them, may be used to objectively measure the participant's status and confirm eligibility for enrollment:

- International Standards for the Neurological Classification of Spinal Cord Injury (INSCI) examination- The ISNCSCI is a standardized assessment used to determine the motor and sensory impairment and severity of a spinal cord injury (previously known as the ASIA examination based on the American Spinal Injury Association).[55]
- Spinal Cord Assessment Tool for Spastic Reflexes (SCATS)- The SCATS is a reliable and valid tool for assessing spasm activity of flexor and extensor muscle groups as well as spastic hypertonia in patients with spinal cord injury.[56]
- Brief Pain Inventory (BPI)- This validated self-report questionnaire assesses pain severity and its impact on function.[57] The BPI items are a more comprehensive measure of pain interference compared to some other measures in the SCI population.[58]
- 10-Meter Walk Test (10MWT)- This validated measures assesses forward walking speed.[59,60]
- Vital signs- To assess participant safety and responses to study procedures, we will monitor blood pressure, heart rate, respiratory rate and pulse oximetry during study procedures. Establishment of baseline readings and monitoring of cardiopulmonary responses will allow for assessment of abnormal responses such as autonomic dysreflexia.[61]

Female subjects of potential childbearing age will be asked to take a pregnancy test. Furthermore, participants will be instructed that they should take precautions against becoming pregnant during the study because the fetal risks associated with tsDCS are unknown. If a participant learns that she is pregnant, she must withdraw from the study immediately. All test outcomes will be recorded on the On-Site Screening Form (see Information Sources and Identifier attachments). If participants complete the on-site screening, are deemed eligible and wish to pursue enrollment in the study, the participant will proceed to the medical screening step. They will also be provided with the informed consent form for the full study (ICF- Intervention) so that they may review this information ahead of time.

Step three- medical screening and physician approval

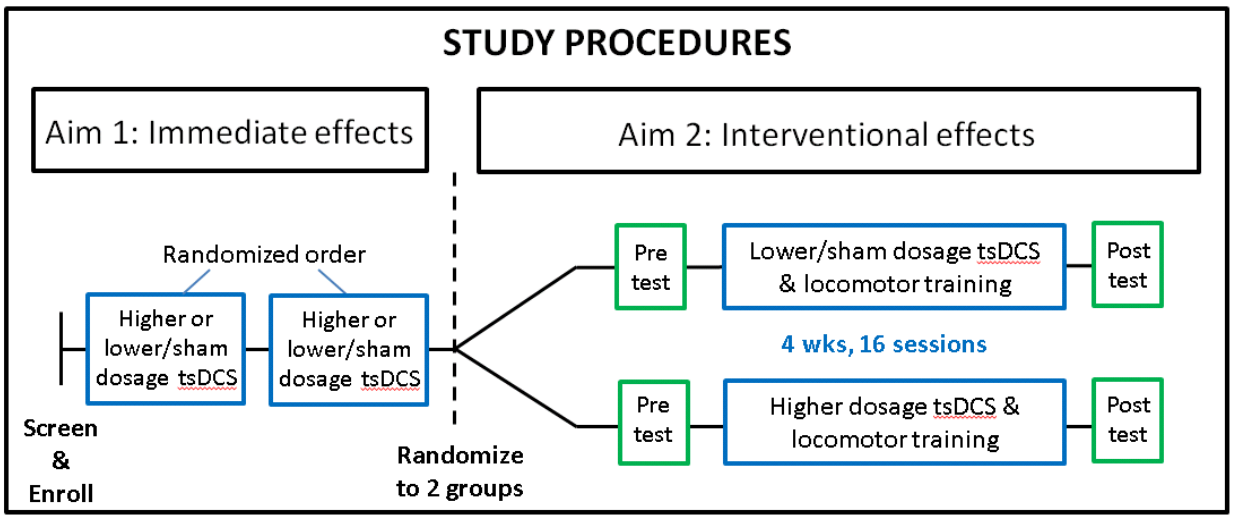
Medical records will be obtained using the Medical Record Authorization form (see Information Sources and Identifier attachments). This form will be provided to the potential participant requesting their date of birth and signature to allow release of their medical records. Once the records are received, study staff will perform a medical record screen using the Medical Record Screening Form (see Information Sources and Identifier attachments) to verify the potential participant meets enrollment criteria. The study physician will oversee this process. In addition to the medical record screen, a written confirmation of medical approval by a physician, using the IRB-approved Physician Approval Letter/Form (see Information Sources and Identifier attachments), also will be required to indicate the potential participant is medically safe to participate in study procedures and does not have known medical conditions that violate the enrollment criteria.

If an individual completes and passes all three steps of the screening process, the participant can then choose to enroll in the full study. The informed consent form (ICF-Intervention) will be provided at the completion of the screening visit to allow potential participants to time to review the document in advance. Generally, the individual will be informed of the study purpose, procedures, possible benefits/risks, the alternatives to being in the study and how the individual's protected health information will be collected, used, and shared with others using the ICF-Intervention as a guide. Participants can either complete the informed consent and begin study procedures on the same day or study staff will schedule a separate time for the individual to complete the informed consent and enroll in the study.

Study Procedures Overview

For Aim 1 (immediate effects of tsDCS), participants will complete two separate testing sessions, presented in random order, that involve up to 30 minutes of tsDCS at one of the two dosages while walking. We will assess changes in muscle activity, kinematics and spinal excitability before and at the end of the period of walking. The two sessions will last about 3 hours and no longer than 6 hours and will take place at least 48 hours apart to allow for wash-out of stimulation effects.

For Aim 2 (effects of tsDCS applied with locomotor training), participants will be randomized to receive 16 sessions of locomotor training with tsDCS at one of the two dosages. Each intervention session will last about 1 hour and no longer than 2.5 hours. Before and after the 16-session intervention (i.e., at baseline and post intervention), we will assess functional outcomes through standardized clinical tests of walking speed and endurance, as well as changes in muscle activity, kinematics and spinal excitability. We will also examine the participant's spasticity and pain using standardized assessments. Each assessment session will last about 3 hours and no longer than 6 hours.



Overall, the testing and intervention procedures of this study will be as follows (see Fig. 1 for details):

1. Aim 1's first visit will consist of clinical testing and collection of basic demographic information (see Information Sources and Identifier attachments for demographics form) to characterize the participant. Neuromechanical assessments of walking and reflex testing prior to and after 30 minutes of tsDCS at one of the two dosages delivered while walking on a treadmill will be conducted.
2. Aim 1's second visit will involve identical procedures for stimulation and neuromechanical assessments as compared to visit 1 except for crossover of the tsDCS dosage. It will also include any clinical testing not completed on day 1.
3. Aim 2's pre-test will consist of neuromechanical assessments of walking and reflex testing as well as clinical assessments of pain, spasticity, and physical function.
4. 16 sessions of locomotor training will be conducted over 4 weeks with one of the two dosages of tsDCS applied during the training.
5. Aim 2's post-test will repeat the measures completed at pre-test.

A physical therapist will oversee study procedures. Vital signs, such as blood pressure, heart rate and blood oxygen saturation, will be monitored for safety. Rest breaks will be provided at regular intervals and at any time the participant requests. Participants will be informed that they may choose not to perform any aspect of the study. We will adjust the assessment protocol, outlined below, as needed in response to our participants, such as reducing the assessments due to fatigue or individual tolerance.

Neuromechanical assessments of walking

Neuromechanical assessments, such as the analysis of muscle activation and movement during walking, will be conducted during testing for both Aim 1 and 2. During Aim 1, the assessments will occur before and after the completion of up to 30 minutes of treadmill walking. As most participants will not tolerate 30 minutes of uninterrupted walking, the session will be divided with rest breaks as needed to deliver a total of ~30 minutes of walking. tsDCS at one of the two dosages will be applied for up to 30 minutes. The goal of the protocol is to complete 30 minutes of walking with stimulation. However, we recognize that this protocol may need to be adjusted slightly for some individuals based on aspects such as comfort or fatigue. During Aim 2, neuromechanical assessments of walking will be conducted before and after the 16 sessions of locomotor training. To perform these neuromechanical assessments, participants may be asked to perform activities such as treadmill walking or overground walking at self-selected or fastest-comfortable walking speeds, walking backward, and stepping over an obstacle. Participants may use any typically used orthotics (i.e. AFOs) or gait assistive devices required by the participant.

All testing procedures will be closely monitored by a physical therapist who will monitor the participant's vital signs for safety and provide rest breaks as needed or requested. A safety harness attached to an overhead support system may be used when performing walking overground. Testing will also occur while walking on a treadmill using a harness to secure the participant to an overhead support system to provide partial body weight support if needed. Participants may opt not to perform any walking task, and all tasks will be adjusted for each participant's functional level. Study procedures will be explained ahead of time and participants will be asked to wear appropriate clothing for participation. Participants will be able to sit comfortably during the set-up procedures. During the set-

up, small reflective markers and EMG sensors will be affixed to the skin and will be removed at the conclusion of the assessment (details below).

The following procedures will be completed during the neuromechanical assessments:

- Measurement of joint motions during standing and walking- To quantify trunk and lower extremity joint motions, a 12-camera three-dimensional motion analysis system will be used to collect marker data and measure joint kinematics during walking tasks.[62] Small, lightweight reflective markers will be placed on the upper and lower extremities and the trunk using an established marker set. To reduce artifact and improve accuracy of motion analysis data, reflective markers will be placed directly on the skin when possible using hypoallergenic double-sided tape. Individuals will be asked to wear tight, minimal clothing, such as tank tops and athletic shorts, to provide access to bony, anatomical landmarks as able.
- Recording of muscle activation- A wireless, 16-channel surface electromyography (EMG) system will be used to record muscle activation during the standing and walking activities. In the small area over the muscle where the sensors will be placed, the skin will be shaved and cleaned with alcohol prior to attaching the sensors with hypoallergenic double-sided tape. These procedures optimize EMG signals by reducing noise and impedance. EMG signals will be recorded using the motion capture software to synchronize collection of the EMGs and motion data (kinematics).
- Assessment of kinetics and spatio-temporal movement characteristics- Ground reaction forces (kinetics) will be recorded during the walking activities. The participants will be asked to walk over the standard built-in force plates, which are flush with the floor and are not an obstacle or tripping hazard. This will be done while they also are wearing the EMGs and reflective markers so that all data are captured simultaneously. During the session, the participant may be asked to stand or walk over a 12' instrumented walkway (i.e. GaitRite). The walkway appears like a flat, carpeted surface and has embedded sensors to record foot falls and foot placement. The edges of the walkway will be taped down to be nearly flush with the floor and to minimize the possibility of tripping. Participants will be guarded at all times and/or an overhead harness may be used. The instrumented walkway will provide quantitative data regarding the spatial and temporal characteristics of standing and walking.
- Recording of cortical activity- Functional near infrared spectroscopy (fNIRS) will be used to assess brain/neural activity required for the individual to perform the standing and walking tasks assessed during the motion capture biomechanical testing. fNIRS uses non-invasive sensors that are light-emitting diodes to illuminate oxygenated hemoglobin in superficial brain tissue.[63] This approach is used to indirectly quantify neural activity. The sensors are attached

to a lightweight strap which will be placed around the participant's forehead to monitor neural activity in the pre-frontal cortex. No skin preparation is required. The data are transmitted wirelessly to a computer to record the data and for future analysis. This information can be used to better understand the cognitive and attentional efforts used while performing the walking tasks, which may relate to safety and fall risk.

Reflex testing

To quantify stimulation induced effects on spinal activation, H-reflex assessment of the soleus muscle will be conducted according to accepted and widely used methodology.[64,65] First, the H-reflex will be recorded while the participant rests in a semi-reclined positioned with the foot supported in slight ankle dorsiflexion (~10 degrees) and the knee in 30 degrees of flexion. Stimulation will be delivered via a cathode placed in the popliteal fossa and an anode placed above the patella. EMGs will be recorded from the soleus with bipolar surface electrodes placed 3 cm apart. M-waves and H-waves will be recorded over a range of intensities to acquire a full recruitment curve, starting at subthreshold intensities and increasing until the reflex amplitude reaches a plateau. The range of intensities is necessary so that a response equivalent to 50% of Hmax can be elicited for use in analyses comparing between individuals.[36] Second, modulation of the H-reflex may be examined during walking. The cathode and anode will be secured with adhesive tape or a self-adhering wrap (e.g., Coband) with care being taken to avoid restricting movement of the knee. Mmax will be re-established in the standing position for analysis of walking H-waves. During walking, stimulation intensity will be adjusted every stimulation to maintain a consistent M-wave amplitude relative to the maximum M-wave (M-max). We will visually determine events of the gait cycle to manually trigger every two to five seconds and collect H-waves during both mid-stance and mid-swing.

The electrical stimulation for H-reflex testing may be uncomfortable at times, but it is not dangerous. The discomfort is temporary and lasts only a few seconds. Evidence of stimulation induced effects on spinal excitability will provide insight into the potential underlying mechanisms mediating changes in muscle activation and limb control during tsDCS and walking.

Clinical assessments

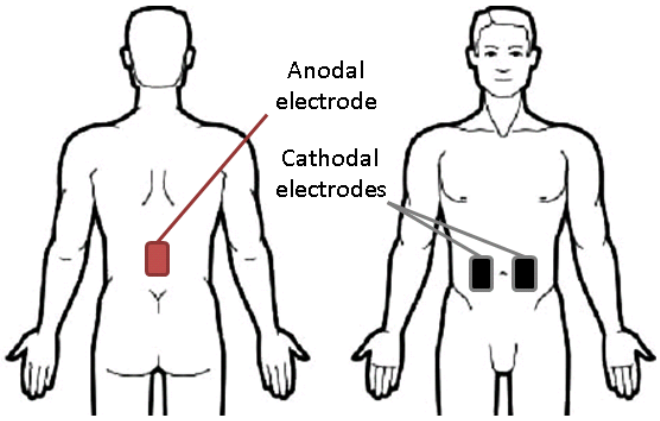
Clinical assessments will be used to characterize the participants during Aim 1 and to examine changes following the regimen of locomotor training in Aim 2. These assessments will include:

- Spinal Cord Assessment Tool for Spastic Reflexes (SCATS)- The SCATS is a reliable and valid tool for assessing spasm activity of flexor and extensor muscle groups as well as spastic hypertonia in patients with spinal cord injury.[56]
- 10-Meter Walk Test (10MWT)- This validated measures assesses forward walking speed.[59,60]
- 6-Minute Walk Test (6MWT)- The 6MWT is a reliable and valid tool for assessing walking endurance.[59,60]

- International Standards for the Neurologic Classification of Spinal Cord Injury (ISNCSCI)- Clinical tests of sensory and motor function to classify level and severity of spinal cord injury (ASIA impairment scale)[55]
- 30-second Chair Stand Test (30-s CST)- Performance assessment to measure functional lower limb muscle strength used to move from sitting to/from standing[66]
- Activities Specific Balance Confidence (ABC) Scale- Questionnaire to assess self-reported balance confidence in varied functional situations such as walking in a parking lot or in the home[67]
- Neuromuscular Recovery Scale (NMRS)- Performance assessment of functional motor recovery such as sitting and standing function[68]
- 3-meter Backward Walk Test- An assessment of backward walking speed[77]
- Postural muscle strength assessment – Seated clinical test of postural muscle strength using hand-held force dynamometry[78]

Delivery of tsDCS

tsDCS will be delivered to the low back, over the lumbar region of the spinal cord, using a commercially available direct current stimulation unit (Soterix Medical Inc). Each tsDCS electrode is comprised of a carbon rubber electrode encased in a saline-soaked sponge. The electrodes will be placed on the participant using a previously established configuration to target the lumbosacral cord with two electrodes on the abdomen placed to the left and right of the umbilicus and one over the lumbar spinal cord at the level of the 11th and 12th thoracic vertebrae. A large elastic bandage with Velcro closure will be wrapped around the abdomen to hold the electrodes firmly in place. Participants will be closely monitored for any adverse responses such as skin irritation and pain. This electrode configuration has been shown to appropriately target the lumbosacral spinal cord, as validated by modeling of electrical current flow[69] and by gains in lower extremity motor performance.[70] A low dosage of ≤ 2.5 mA stimulus will be used for the "higher" dosage. This dosage (or very similar) has been used in numerous prior studies and has been shown to be well-tolerated and to produce measurable changes in reflex activity and/or lower extremity motor performance.[18,20,21,36,47,70,71] An identical montage and stimulation arrangement will be used for the "lower" dosage, except the stimulation will be delivered in a brief ramp-like manner for 30 seconds at the beginning and end of the stimulation period. The "lower" dosage condition is effectively a "sham" procedure. This approach is widely used in the field of direct current stimulation, and has been reported to be indistinguishable from the "higher" dosage protocol.[20,72] This is because participants quickly habituate to the sensation of active stimulation. To assess the effectiveness of our low dose/sham stimulation, participants will be asked during Aim 2 post-testing which



dosage they believe they received and how certain they are of their opinion. They will then be informed which dosage they received.

Locomotor training

Participants will be randomized to either the combined intervention of higher dosage tsDCS with locomotor training or lower dosage tsDCS with locomotor training. Each participant will receive up to 16 sessions of training with each session including up to 40 minutes of walking. The goal is to have participants attend 4 sessions per week for 4 weeks, but the individual schedules might vary. All sessions will be led by a licensed physical therapist with experience in walking rehabilitation after ISCI. There will be two components to the locomotor training session: 1) body-weight supported treadmill locomotor training with tsDCS (LT-TM) and 2) overground walking without tsDCS (OG).

1) LT-TM (30 min): This portion of the intervention will consist of 30 minutes of locomotor training on a treadmill and will follow standard procedures for body-weight supported treadmill locomotor training that have been published by our group and others.[3,4,25,73] tsDCS, as described above, will be applied during body-weight supported treadmill locomotor training. Briefly, participants will walk on a treadmill with verbal feedback and manual assistance provided by training staff. This assistance is provided as needed to help move the leg during stepping and/or to maintain stability and balance. Avoidance of falls is assured while walking on the treadmill by an overhead body weight support safety attached to a trunk/pelvis harness. Body weight support will be set low as possible in order to allow balance responses and to afford support only as needed. Performance without compensation strategies (hip hiking, leaning to one side) will be emphasized. Rest breaks will be provided as needed.

   The physical therapist leading the training will monitor for both safety and intensity of training. Self-reported level of exertion, based on the Borg scale, will be recorded. A chest-worn heart rate monitor will be used to ensure sufficient training intensities by encouraging participants to maintain a training heart rate between 70-80% of their predicted maximal heart rate. Based on this, the target training heart rate will be calculated as (220 – age) * 70. Furthermore, the duration of stepping will be tracked and step counts will be measured using an ankle-worn accelerometer.[25,74-76] This heart rate range is based on recent evidence indicating that this intensity is safe and tolerated, and is an important factor associated with gains in locomotor function.[74] Locomotor training parameters, such as walking speed, level of assistance, treadmill incline, body weight support and frequency of rest breaks will be adjusted as needed to respond to the participant's exercise tolerance and to advance the training as appropriate. A record of both training parameters and participant response will be kept in the Daily Training Log (see Information Sources and Identifier attachments). All training parameters will be adjusted for participant's tolerance, comfort and safety.

2) OG (10 min): After completing the training portion described above, the tsDCS will be removed and the participant will then practice walking overground for

approximately 10 minutes. Assistance of trainers will be provided as needed and the participant may use assistive device or orthotics. Rest breaks may be taken at any time.

The intervention sessions will aim to include a total of 40 minutes of stepping time, which may take up to 2 hours to complete due to set up time and rest breaks.

Statistical Plan

A descriptive analysis of demographic data and injury characteristics will be conducted using a frequency distribution for categorical data and means for continuous variables. These data will be used to characterize general information about the study population. Sample size and data distribution will guide statistical analysis. If data assumptions are achieved, for Aim 1, we will determine the effects of tsDCS during walking using two-way repeated measures ANOVAs. The within factors will be time (before or at the end of walking bout) and stimulation (higher or lower dosage tsDCS). We will then examine the interaction effect to determine differences in the changes during walking with the two dosages of tsDCS. For Aim 2, mixed method ANOVAs will be used to determine the effects of tsDCS dosage during locomotor training. The within factor will be time (pre- or post-test) and between factor will be group (higher or lower dosage tsDCS). We will then examine the interaction effect to determine differences in the improvement during locomotor training with the two dosages of tsDCS. Differences will be considered significant at $p<.05$. Data will be analyzed using professional statistical software.

Safety monitoring

Although numerous studies indicate tsDCS is easily tolerated and no adverse responses have been reported,[15,51] we will closely monitor participant responses. At each session the participant and physical therapist will complete a questionnaire to document any side effects such as stimulation site discomfort or skin irritation. While we do not expect any issues, we will monitor the skin closely. If any changes are observed beyond mild redness or if persistent discomfort is reported, stimulation intensity will be reduced (or discontinued, if necessary) during that training session and increased to 2.5mA in subsequent sessions if tolerated. Irritation could also occur if the harness is not fitted or positioned correctly, so this will be closely monitored and adjustments will be made as needed. In accordance with University of Florida IRB policy, adverse events that are both unexpected and serious will be reported within 5 working days.

The testing and intervention procedures could be tiring for some individuals. All participants will be given rest breaks and informed that they may rest or terminate their participation at any time. Blood pressure (BP) and heart rate (HR) will be monitored during each testing and intervention session. BP and HR must be within a medically-acceptable range for the participant to participate in a testing or training session. Resting diastolic BP must be less than 100mmHg to begin the session. The criteria for termination include complaints or symptoms of confusion, dyspnea, onset of angina, excessive blood pressure changes (systolic BP greater than 200mmHg or diastolic BP greater than 110mmHg). In addition, should the participant's HR exceed 85% of the predicted maximum HR or the participant reports a Borg rating of perceived exertion (RPE) rate of greater than 17/20, then the session will be slowed and/or halted. If the session is halted,

the participant will be asked to rest while BP and HR are monitored and will resume only when BP and HR return to acceptable values and the participant reports no other symptoms. If any of these conditions persist after rest, the participant's primary physician and/or the study physician may be contacted and the participant may be referred for evaluation. If the participant complains of angina at rest, loss of consciousness occurs, or cardiac arrest, emergency medical services through 911 will be called immediately.

7. **Possible Discomforts and Risks:**

During the testing procedures, participants may become fatigued. Participants will be allowed to rest at any time. To prevent falls, a harness attached to an overhead support system may be used during overground testing procedures with any individual that requires assistance or who is unsteady. A harness with overhead support will be used for any testing that occurs on the treadmill. Despite these safety measures, as with any walking activity, there is a risk that participants may lose their balance, stumble or fall and experience an injury. While the harness will prevent falling to the ground, it is still possible for participants to experience an injury due to the harness catching their body weight during the potential fall.

The proposed assessments are routine and pose minimal risk to study participants. These techniques have been used extensively for many years in those with functional impairments without significant occurrence of adverse events. Fatigue may occur due to physical exertion associated with testing, and could result in muscle soreness, but this is a normal and temporary response to unaccustomed activity. Sufficient rest will be provided to minimize discomfort for participants. Also, heart rate and blood pressure will be monitored during testing, as well as signs of autonomic dysreflexia. As noted in the "safety monitoring" section above, there is a slight risk of stimulation site discomfort or skin irritation from the tsDCS, which will be monitored and adjustments to stimulation intensity will be made if necessary. Furthermore, transient discomfort may be caused during H reflex testing. There is a slight risk of skin irritation with the use of surface EMG electrodes, markers and tape. To avoid skin irritation, hypoallergenic tape will be used and the participants' skin will be inspected periodically during testing procedures.

Some participants may not feel comfortable responding to the questionnaires or telling research personnel that they are uncomfortable or fearful of performing a certain activity. All questionnaires will be administered in-private with only the research personnel and the participant. Participants will be instructed that they do not need to complete the questionnaires if they prefer not to. The participant will be informed that they may opt not to participate in any of the study procedures.

During the intervention sessions, the participants may also experience fatigue while performing locomotor training. While similar to walking, this training occurs at a higher intensity to promote neuromuscular changes. The participants will be allowed to rest at any time and rest breaks will be incorporated at regular intervals. The risks in undergoing locomotor training are minimal and include a loss of balance while walking, a risk of injury from falls while walking, experience of an elevated heart rate with exercise, temporary muscle fatigue, nervousness when attempting to walk while on the treadmill or off the treadmill, muscle strains or sprains, skin irritation from wearing a harness, and skin

irritation from contact with the trainer's hands assisting leg movement. Heart rate and blood pressure will be checked regularly throughout each session. Participants will be monitored for signs and symptoms of autonomic dysreflexia such as high blood pressure, flushing and profuse sweating above the level of injury with piloerection and paleness below the level of injury, and/or intense headache. Study activities will be carried out with the close supervision of a physical therapist and a harness with overhead support will be used at all times. As noted above, there could be discomfort or injury associated with the harness catching their body weight if a stumble or loss of balance occurs while walking in the harness. Parameters of the locomotor training sessions will be adjusted to ensure comfort and safety.

Confidentiality and protecting subject privacy

The risks related to collecting and sharing protected health information and study-related data will be addressed in several ways. First, upon enrollment in the study, a study ID will be assigned to the participant so that all study-related information pertaining to the subject uses the study ID. The document that links study-IDs to participant information will be stored in a separate location, not with the study-related data. The study procedures will be conducted in private locations at Brooks Rehabilitation, so that participant privacy may be maintained when conducting procedures such as clinical testing, administering questionnaires, or answering individual questions. All study procedures will be conducted in limited access areas with minimal traffic and personnel.

Protected health information collected as part of this study will be limited to the minimal necessary information to carry out procedures in this approved protocol. All hard-copy study related documents will be stored in locked file cabinets in locked offices. All electronic study related information and data will be stored on password protected computers and on password-protected institutional servers or encrypted electronic storage devices. Only approved study personnel will have access to research records.

For participants who provided consent for photography and/or video, recordings or photographs may be obtained during their session. Recordings or photographs will only occur based on the consent provided by each participant. The participant will be informed that they may refuse the use of photography or video recordings at any time during the procedures. All photographs and videos will be acquired digitally, and stored on computer servers with secure passwords, or encrypted electronic storage devices. Photographs and/or videos will only be used in the manner that the subject consents to, as indicated on the Informed Consent Form (i.e., photos/videos must be destroyed once the study is closed; photos/videos may be used as described in the Informed Consent Form, and for the purposes of education at UF; or, as described in the ICF, for the purposes of education at UF, and for presentations at scientific meetings outside of UF). Photos/videos will be used by the study team to review and share study procedures, methods, and dissemination of study findings. Videos may also be used to ensure consistency of study procedures.

8. Possible Benefits:

Health:

Each participant may or may not benefit from this study. The possible benefits are that the participant may experience improvements in walking function. These improvements may include increased walking speed, endurance, or increased movement coordination. The participant's balance may improve and they may become more confident in their balance and walking ability. Overall ability to perform daily functional activities may or may not improve. Such improvements may result from increased standing and walking function and/or increased cardiovascular function secondary to daily exercise (i.e. 30 min of locomotor training).

Financial:

Participants will be compensated $20 for each Aim 1 session, $20 each for the Aim 2 pre-test and post-test and $10 for each Aim 2 intervention session. Payment will be issued using a gift card to participants. Thus, upon full completion of all visits, subjects will have been provided with $240.00 for their participation in the study. This compensation is for the participant's time and travel to complete the study. Compensation will be pro-rated and the participant will be paid on a weekly basis. Participants will not need to complete the study to receive payment.

9. Conflict of Interest:

There are no conflicts of interests relating to any of the investigators and this protocol beyond the professional benefit from academic publication or presentation of the results.

References Cited

1. Behrman AL, Harkema SJ. Locomotor training after human spinal cord injury: a series of case studies. *Physical therapy.* Jul 2000;80(7):688-700.
2. Field-Fote EC, Roach KE. Influence of a locomotor training approach on walking speed and distance in people with chronic spinal cord injury: a randomized clinical trial. *Physical therapy.* Jan 2011;91(1):48-60.
3. Fox EJ, Tester NJ, Phadke CP, et al. Ongoing walking recovery 2 years after locomotor training in a child with severe incomplete spinal cord injury. *Physical therapy.* May 2010;90(5):793-802.
4. Harkema SJ, Hillyer J, Schmidt-Read M, Ardolino E, Sisto SA, Behrman AL. Locomotor training: as a treatment of spinal cord injury and in the progression of neurologic rehabilitation. *Archives of physical medicine and rehabilitation.* Sep 2012;93(9):1588-1597.
5. Edgerton VR, Tillakaratne NJ, Bigbee AJ, de Leon RD, Roy RR. Plasticity of the spinal neural circuitry after injury. *Annual review of neuroscience.* 2004;27:145-167.
6. Harkema SJ. Plasticity of interneuronal networks of the functionally isolated human spinal cord. *Brain Res Rev.* Jan 2008;57(1):255-264.
7. Behrman AL, Lawless-Dixon AR, Davis SB, et al. Locomotor training progression and outcomes after incomplete spinal cord injury. *Physical therapy.* Dec 2005;85(12):1356-1371.
8. Wirz M, Zemon DH, Rupp R, et al. Effectiveness of automated locomotor training in patients with chronic incomplete spinal cord injury: a multicenter trial. *Archives of physical medicine and rehabilitation.* Apr 2005;86(4):672-680.
9. Dobkin B, Apple D, Barbeau H, et al. Weight-supported treadmill vs over-ground training for walking after acute incomplete SCI. *Neurology.* Feb 28 2006;66(4):484-493.
10. Angeli CA, Edgerton VR, Gerasimenko YP, Harkema SJ. Altering spinal cord excitability enables voluntary movements after chronic complete paralysis in humans. *Brain : a journal of neurology.* May 2014;137(Pt 5):1394-1409.
11. Rejc E, Angeli CA, Atkinson D, Harkema SJ. Motor recovery after activity-based training with spinal cord epidural stimulation in a chronic motor complete paraplegic. *Scientific reports.* Oct 26 2017;7(1):13476.
12. Edgerton VR, Leon RD, Harkema SJ, et al. Retraining the injured spinal cord. *J Physiol.* May 15 2001;533(Pt 1):15-22.
13. Roy RR, Harkema SJ, Edgerton VR. Basic concepts of activity-based interventions for improved recovery of motor function after spinal cord injury. *Arch Phys Med Rehabil.* Sep 2012;93(9):1487-1497.
14. Cogiamanian F, Vergari M, Schiaffi E, et al. Transcutaneous spinal cord direct current stimulation inhibits the lower limb nociceptive flexion reflex in human beings. *Pain.* Feb 2011;152(2):370-375.
15. Nardone R, Holler Y, Taylor A, et al. Noninvasive Spinal Cord Stimulation: Technical Aspects and Therapeutic Applications. *Neuromodulation : journal of the International Neuromodulation Society.* Oct 2015;18(7):580-591; discussion 590-581.
16. Ahmed Z. Trans-spinal direct current stimulation modulates motor cortex-induced muscle contraction in mice. *Journal of applied physiology.* May 2011;110(5):1414-1424.
17. Ahmed Z. Effects of cathodal trans-spinal direct current stimulation on mouse spinal network and complex multijoint movements. *The Journal of neuroscience : the official journal of the Society for Neuroscience.* Sep 11 2013;33(37):14949-14957.
18. Cogiamanian F, Vergari M, Pulecchi F, Marceglia S, Priori A. Effect of spinal transcutaneous direct current stimulation on somatosensory evoked potentials in humans. *Clin Neurophysiol.* Nov 2008;119(11):2636-2640.

19. Ahmed Z. Modulation of gamma and alpha spinal motor neurons activity by trans-spinal direct current stimulation: effects on reflexive actions and locomotor activity. *Physiological reports.* Feb 2016;4(3).
20. Hubli M, Dietz V, Schrafl-Altermatt M, Bolliger M. Modulation of spinal neuronal excitability by spinal direct currents and locomotion after spinal cord injury. *Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology.* Jun 2013;124(6):1187-1195.
21. Bocci T, Marceglia S, Vergari M, et al. Transcutaneous spinal direct current stimulation modulates human corticospinal system excitability. *Journal of neurophysiology.* Jul 2015;114(1):440-446.
22. Bocci T, Vannini B, Torzini A, et al. Cathodal transcutaneous spinal direct current stimulation (tsDCS) improves motor unit recruitment in healthy subjects. *Neuroscience letters.* Aug 22 2014;578:75-79.
23. Field-Fote EC, Lindley SD, Sherman AL. Locomotor training approaches for individuals with spinal cord injury: a preliminary report of walking-related outcomes. *Journal of neurologic physical therapy : JNPT.* Sep 2005;29(3):127-137.
24. Field-Fote EC, Tepavac D. Improved intralimb coordination in people with incomplete spinal cord injury following training with body weight support and electrical stimulation. *Physical therapy.* Jul 2002;82(7):707-715.
25. Fox EJ, Tester NJ, Butera KA, et al. Retraining walking adaptability following incomplete spinal cord injury. *Spinal cord series and cases.* 2017;3:17091.
26. Grasso R, Ivanenko YP, Zago M, Molinari M, Scivoletto G, Lacquaniti F. Recovery of forward stepping in spinal cord injured patients does not transfer to untrained backward stepping. *Experimental brain research.* Aug 2004;157(3):377-382.
27. Wernig A, Muller S. Laufband locomotion with body weight support improved walking in persons with severe spinal cord injuries. *Paraplegia.* Apr 1992;30(4):229-238.
28. Edgerton VR, Roy RR, Hodgson JA, Prober RJ, de Guzman CP, de Leon R. A physiological basis for the development of rehabilitative strategies for spinally injured patients. *The Journal of the American Paraplegia Society.* Oct 1991;14(4):150-157.
29. Dietz V. Interaction between central programs and afferent input in the control of posture and locomotion. *J. Biomech.* Jul 1996;29(7):841-844.
30. Hiebert GW, Pearson KG. Contribution of sensory feedback to the generation of extensor activity during walking in the decerebrate Cat. *Journal of neurophysiology.* Feb 1999;81(2):758-770.
31. Hiebert GW, Whelan PJ, Prochazka A, Pearson KG. Contribution of hind limb flexor muscle afferents to the timing of phase transitions in the cat step cycle. *Journal of neurophysiology.* Mar 1996;75(3):1126-1137.
32. Maegele M, Muller S, Wernig A, Edgerton VR, Harkema SJ. Recruitment of spinal motor pools during voluntary movements versus stepping after human spinal cord injury. *J Neurotrauma.* Oct 2002;19(10):1217-1229.
33. McVea DA, Donelan JM, Tachibana A, Pearson KG. A role for hip position in initiating the swing-to-stance transition in walking cats. *Journal of neurophysiology.* Nov 2005;94(5):3497-3508.
34. Pearson KG. Role of sensory feedback in the control of stance duration in walking cats. *Brain Res Rev.* Jan 2008;57(1):222-227.
35. Gomes-Osman J, Field-Fote EC. Cortical vs. afferent stimulation as an adjunct to functional task practice training: a randomized, comparative pilot study in people with cervical spinal cord injury. *Clinical rehabilitation.* Aug 2015;29(8):771-782.
36. Lamy JC, Ho C, Badel A, Arrigo RT, Boakye M. Modulation of soleus H reflex by spinal DC stimulation in humans. *Journal of neurophysiology.* Aug 1 2012;108(3):906-914.

37. Hofstoetter US, Krenn M, Danner SM, et al. Augmentation of Voluntary Locomotor Activity by Transcutaneous Spinal Cord Stimulation in Motor-Incomplete Spinal Cord-Injured Individuals. *Artificial organs.* Oct 2015;39(10):E176-186.
38. Ahmed Z. Electrophysiological characterization of spino-sciatic and cortico-sciatic associative plasticity: modulation by trans-spinal direct current and effects on recovery after spinal cord injury in mice. *The Journal of neuroscience : the official journal of the Society for Neuroscience.* Mar 13 2013;33(11):4935-4946.
39. Cogiamanian F, Ardolino G, Vergari M, et al. Transcutaneous spinal direct current stimulation. *Frontiers in psychiatry.* 2012;3:63.
40. Hubli M, Dietz V. The physiological basis of neurorehabilitation--locomotor training after spinal cord injury. *Journal of neuroengineering and rehabilitation.* Jan 21 2013;10:5.
41. Murray LM, Tahayori B, Knikou M. Transspinal Direct Current Stimulation Produces Persistent Plasticity in Human Motor Pathways. *Scientific reports.* Jan 15 2018;8(1):717.
42. Dietz V, Grillner S, Trepp A, Hubli M, Bolliger M. Changes in spinal reflex and locomotor activity after a complete spinal cord injury: a common mechanism? *Brain : a journal of neurology.* Aug 2009;132(Pt 8):2196-2205.
43. Hubli M, Dietz V, Bolliger M. Spinal reflex activity: a marker for neuronal functionality after spinal cord injury. *Neurorehabilitation and neural repair.* Feb 2012;26(2):188-196.
44. Nielsen J, Petersen N, Crone C. Changes in transmission across synapses of Ia afferents in spastic patients. *Brain : a journal of neurology.* Aug 1995;118 (Pt 4):995-1004.
45. Phadke CP, Thompson FJ, Kukulka CG, et al. Soleus H-reflex modulation after motor incomplete spinal cord injury: effects of body position and walking speed. *The journal of spinal cord medicine.* 2010;33(4):371-378.
46. Phadke CP, Wu SS, Thompson FJ, Behrman AL. Comparison of soleus H-reflex modulation after incomplete spinal cord injury in 2 walking environments: treadmill with body weight support and overground. *Arch Phys Med Rehabil.* Dec 2007;88(12):1606-1613.
47. Winkler T, Hering P, Straube A. Spinal DC stimulation in humans modulates post-activation depression of the H-reflex depending on current polarity. *Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology.* Jun 2010;121(6):957-961.
48. Trimble MH, Behrman AL, Flynn SM, Thigpen MT, Thompson FJ. Acute effects of locomotor training on overground walking speed and H-reflex modulation in individuals with incomplete spinal cord injury. *The journal of spinal cord medicine.* Summer 2001;24(2):74-80.
49. Trimble MH, Kukulka CG, Behrman AL. The effect of treadmill gait training on low-frequency depression of the soleus H-reflex: comparison of a spinal cord injured man to normal subjects. *Neuroscience letters.* May 1 1998;246(3):186-188.
50. Knikou M, Smith AC, Mummidisetty CK. Locomotor training improves reciprocal and nonreciprocal inhibitory control of soleus motoneurons in human spinal cord injury. *J Neurophysiol.* Apr 1 2015;113(7):2447-2460.
51. Priori A, Ciocca M, Parazzini M, Vergari M, Ferrucci R. Transcranial cerebellar direct current stimulation and transcutaneous spinal cord direct current stimulation as innovative tools for neuroscientists. *J Physiol.* Aug 15 2014;592(16):3345-3369.
52. Brunoni AR, Boggio PS, De Raedt R, et al. Cognitive control therapy and transcranial direct current stimulation for depression: a randomized, double-blinded, controlled trial. *Journal of affective disorders.* Jun 2014;162:43-49.
53. Dedoncker J, Brunoni AR, Baeken C, Vanderhasselt MA. A Systematic Review and Meta-Analysis of the Effects of Transcranial Direct Current Stimulation (tDCS) Over the

Dorsolateral Prefrontal Cortex in Healthy and Neuropsychiatric Samples: Influence of Stimulation Parameters. *Brain stimulation.* Jul-Aug 2016;9(4):501-517.
54. Elmasry J, Loo C, Martin D. A systematic review of transcranial electrical stimulation combined with cognitive training. *Restorative neurology and neuroscience.* 2015;33(3):263-278.
55. Kirshblum SC, Burns SP, Biering-Sorensen F, et al. International standards for neurological classification of spinal cord injury (revised 2011). *The journal of spinal cord medicine.* Nov 2011;34(6):535-546.
56. Benz EN, Hornby TG, Bode RK, Scheidt RA, Schmit BD. A physiologically based clinical measure for spastic reflexes in spinal cord injury. *Arch Phys Med Rehabil.* Jan 2005;86(1):52-59.
57. Keller S, Bann CM, Dodd SL, Schein J, Mendoza TR, Cleeland CS. Validity of the brief pain inventory for use in documenting the outcomes of patients with noncancer pain. *The Clinical journal of pain.* Sep-Oct 2004;20(5):309-318.
58. Bryce TN, Budh CN, Cardenas DD, et al. Pain after spinal cord injury: an evidence-based review for clinical practice and research. Report of the National Institute on Disability and Rehabilitation Research Spinal Cord Injury Measures meeting. *The journal of spinal cord medicine.* 2007;30(5):421-440.
59. Scivoletto G, Tamburella F, Laurenza L, Foti C, Ditunno JF, Molinari M. Validity and reliability of the 10-m walk test and the 6-min walk test in spinal cord injury patients. *Spinal cord.* Jun 2011;49(6):736-740.
60. van Hedel HJ, Dietz V, Curt A. Assessment of walking speed and distance in subjects with an incomplete spinal cord injury. *Neurorehabilitation and neural repair.* Jul-Aug 2007;21(4):295-301.
61. Krassioukov A. Autonomic dysreflexia in acute spinal cord injury: incidence, mechanisms, and management. *SCI nursing : a publication of the American Association of Spinal Cord Injury Nurses.* Winter 2004;21(4):215-216.
62. Aggarwal JK, Cai Q. Human motion analysis: A review. *Computer Vision and Image Understanding.* Mar 1999;73(3):428-440.
63. Ferrari M, Quaresima V. A brief review on the history of human functional near-infrared spectroscopy (fNIRS) development and fields of application. *NeuroImage.* Nov 1 2012;63(2):921-935.
64. Tucker KJ, Tuncer M, Turker KS. A review of the H-reflex and M-wave in the human triceps surae. *Human movement science.* Oct-Dec 2005;24(5-6):667-688.
65. Phadke CP, Thompson FJ, Trimble MH, Behrman AL, Kukulka CG. Reliability of soleus H-reflexes in standing and walking post-incomplete spinal cord injury. *The International journal of neuroscience.* Feb 2010;120(2):128-136.
66. Jones CJ, Rikli RE, Beam WC. A 30-s chair-stand test as a measure of lower body strength in community-residing older adults. *Research quarterly for exercise and sport.* Jun 1999;70(2):113-119.
67. Hatch J, Gill-Body KM, Portney LG. Determinants of balance confidence in community-dwelling elderly people. *Phys Ther.* Dec 2003;83(12):1072-1079.
68. Tester NJ, Lorenz DJ, Suter SP, et al. Responsiveness of the Neuromuscular Recovery Scale During Outpatient Activity-Dependent Rehabilitation for Spinal Cord Injury. *Neurorehabilitation and neural repair.* Jul 2016;30(6):528-538.
69. Parazzini M, Fiocchi S, Liorni I, et al. Modeling the current density generated by transcutaneous spinal direct current stimulation (tsDCS). *Clin Neurophysiol.* Nov 2014;125(11):2260-2270.
70. Berry HR, Tate RJ, Conway BA. Transcutaneous spinal direct current stimulation induces lasting fatigue resistance and enhances explosive vertical jump performance. *PloS one.* 2017;12(4):e0173846.

71. Powell ES, Carrico C, Raithatha R, Salyers E, Ward A, Sawaki L. Transvertebral direct current stimulation paired with locomotor training in chronic spinal cord injury: A case study. *NeuroRehabilitation.* 2016;38(1):27-35.
72. Picelli A, Chemello E, Castellazzi P, et al. Combined effects of transcranial direct current stimulation (tDCS) and transcutaneous spinal direct current stimulation (tsDCS) on robot-assisted gait training in patients with chronic stroke: A pilot, double blind, randomized controlled trial. *Restorative neurology and neuroscience.* 2015;33(3):357-368.
73. Routson RL, Clark DJ, Bowden MG, Kautz SA, Neptune RR. The influence of locomotor rehabilitation on module quality and post-stroke hemiparetic walking performance. *Gait & posture.* Jul 2013;38(3):511-517.
74. Brazg G, Fahey M, Holleran CL, et al. Effects of Training Intensity on Locomotor Performance in Individuals With Chronic Spinal Cord Injury: A Randomized Crossover Study. *Neurorehabilitation and neural repair.* Oct-Nov 2017;31(10-11):944-954.
75. Lang CE, Lohse KR, Birkenmeier RL. Dose and timing in neurorehabilitation: prescribing motor therapy after stroke. *Current opinion in neurology.* Dec 2015;28(6):549-555.
76. Yang JF, Musselman KE, Livingstone D, et al. Repetitive mass practice or focused precise practice for retraining walking after incomplete spinal cord injury? A pilot randomized clinical trial. *Neurorehabilitation and neural repair.* May 2014;28(4):314-324.
77. Rose DK, DeMark L, Fox EJ, Clark DJ, Wdyluka P. A backward walking training program to improve balance and mobility in acute stroke: A pilot randomized controlled trial. J Neurol Phys Ther. 2018 Jan;42(1);12-21.
78. Larson CA, Tezak WD, Malley MS, Thornton W. Assessment of postural muscle strength in sitting: reliability of measures obtained with hand-held dynamometry in individuals with spinal cord injury. J Neurol Phys Ther. 2010;34:24-31.