Effects of trans-cutaneous spinal direct current stimulation in incomplete spinal cord injury

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PROTOCOL TITLE: Effects of trans-cutaneous spinal direct current stimulation in incomplete spinal cord injury

2. BACKGROUND and SIGNIFICANCE

According to the National Spinal Cord Injury Statistical Center, as many as 300,000 people in the United States are living with spinal cord injury (SCI), with approximately 17,000 new cases each year.[1] Unfortunately, efforts to minimize neurologic damage in acute SCI have met with only limited success.[2, 3] Complete recovery is reported in less than 1% of SCI survivors.[1] Thus, there is a need for interventions to enhance recovery of function for people living with chronic effects of SCI. Recovery of motor function after chronic SCI has been associated with neuroplastic changes.[4, 5]

Transcranial direct current stimulation has been shown to significantly influence corticomotor excitability (a marker of neuroplasticity).[6-9] The polarity of the current is important in direct current stimulation: anodal stimulation over the primary motor cortex leads to a depolarization of the neuronal membrane's resting potential and thus increases motor cortical excitability; cathodal stimulation causes the opposite effect.[10-12] Early human and animal studies suggest similar modulation of spinal cord excitability after transcutaneous spinal direct current stimulation (tsDCS). Possible mechanisms include alteration of GABAergic and glutamatergic systems.[13-22] However, data in this regard is very limited and inconsistent.[18, 19, 22, 23] This study addresses this gap in research by conducting a exploratory project that will evaluate the effects of tsDCS on spinal excitability. This pilot study will provide preliminary support and effect sizes that will be used in a larger federally funded study

Many symptoms and signs of SCI, such as hyperreflexia and spasticity are associated with H-reflex alteration.[24] Therefore, demonstrating changes in the amplitude of H reflexes might be of potential clinical importance since these changes have been related to the acquisition of new motor skills and in restoration of motor functions in both animals and humans.[25-29] The H-reflex is used commonly to study the excitability of spinal motor circuitry as a surrogate for functional adaptation and neuroplastic changes that may occur in relation to injury, disease, or therapeutic interventions.[26, 30-32] Thus, given the previous finding that tsDCS can alter H reflex[22] we hypothesize that tsDCS is capable of inducing plastic changes of excitability in the monosynaptic pathway mediating the H-reflex, when tested using stimulation rates at which post-activation depression is present.

SSEPs after stimulation of posterior tibial nerve are absent in complete lesions of the spinal cord. However, incomplete lesions yield varying abnormalities on SSEPs. Latencies and amplitudes of tibial SSEPs can change over time after spinal cord injury (SCI). SSEPs have been studied as a surrogate measure to evaluate for neuroplasticity after cortical and spinal

cord stimulation.[17, 33, 34] However, there are no robust studies that evaluated effects of tsDCS on SSEPs.

In sum, and in contrast to most other studies of tsDCS, our design expedites early-stage investigation of this promising intervention by establishing strong, electrophysiological data prior to rapid clinical translation of findings. In general, our proposal has exceedingly high translational potential. The non-invasive stimulation we propose (tsDCS) is delivered by a portable device that can be easily carried and applied in a diversity of clinical settings, including inpatient and outpatient rehabilitation.

3. PURPOSE OF THE STUDY:

The purpose of the study is to investigate the effects of a novel therapeutic approach to promote functional recovery and spasticity in chronic SCI. We will evaluate tsDCS effect on neuro-physiological measure such as H reflex and SSEP in subjects with SCI. This incremental, design will allow us to establish strong, electrophysiological data prior to rapid clinical translation of our findings about this promising, early-stage technique.

The central hypothesis is twofold: 1) active tsDCS will lead to a change in Hmax/M max ratio than sham tsDCS, in a polarity dependent manner; and 2) active tsDCS will lead to a change in SSEP amplitude and latency, in a polarity dependent manner.

Hypothesis: To evaluate the effects of tsDCS and different polarities on spinal excitability as measured by change in Hmax/M max ratio and SSEPs.

Hypothesis 1: In subjects with motor incomplete SCI, either anodal or cathodal tsDCS placed at the T10-T11 level will result in a change in spinal excitability evident by change in Hmax/M max ratio.

Hypothesis 2: In subjects with motor incomplete SCI, either anodal or cathodal tsDCS placed at the T10-T11 level will result in a change in spinal excitability evident by change in somatosensory evoked potential (SSEP).

4. DESCRIPTION OF STUDY:

Subjects will be screened in the outpatient SCI clinic. Each subject will receive five tsDCS (2 cathodal, 2 anodal and 1 sham) conditions at T10-T11 spinal level in a random order. There will be a wash-out period of 1 week between each tsDCS condition. Saline soaked sponge electrodes (36 cm2) will be used to deliver active tsDCS over skin at specified level. Reference electrode will be placed over left shoulder. Active tsDCS (i.e., anodal or cathodal; not sham) will consist of stimulation at an intensity of 2.5 mA for the entirety of each stimulation session (i.e., 2.5mA for 15 minutes to result in a current density of 0.071mA/cm2 and a total delivered charge of 0.064C/cm2). This current density was proven to be safe and sufficient to induce

physiological changes in previous human studies.[17, 19, 35] In a study done on healthy subjects (Korupolu PI), current densities above this range resulted in skin blisters. For sham tsDCS, we will start at 0mA and ramp the intensity up, then down, over a 30-second window. This protocol has proven effectiveness for blinding subjects in studies applying direct current stimulation.

Pre-screening: During the pre-screening process, potential subjects with incomplete SCI will be contacted by phone or in person by Dr. Korupolu (PI) or other co-investigators. Dr.Korupolu will give final approval for the subject to come to The Institute for Rehabilitation and Research Memorial Hermann for the screening procedure.

Screening (Visit 1, duration: One hour): This visit will occur the same day as intervention visit. After subject arrives at TIRR a research personnel will meet him/her at the Motor Recovery Laboratory. The details of the study- specific procedures will be reviewed with the subject together. Subject will be screened for inclusion and exclusion criteria. Signed and dated informed consent will be obtained. Demographics, medical history, list of medications and modified ashworth scale score will be recorded. If the subject is female in child bearing ages, a urine pregnancy test results from primary care physician will be requested. A medication diary will be given to the subject and asked to document all changes in type and dosage of the medication he/she has been using throughout the study. This will allow us to differentiate a potential effect of a change in dosage or type of medication on movement recovery. After subject meets all Inclusion an Exclusion Criteria the randomization will be done by means of sealed, opaque, consecutively numbered envelopes constructed by the research assistant. Each envelope will have intervention sequence information. Sequence will be generated by a random number generator. The research assistant will assign 1 envelope to each subject randomly. Each envelope will be opened by the research assistant prior to first session who will administer tsDCS. The research assistant will not be involved in data analysis or measurement of outcomes.

Intervention (duration: three hours): This visit is divided in to baseline, tsDCS stimulation and post tsDCS.

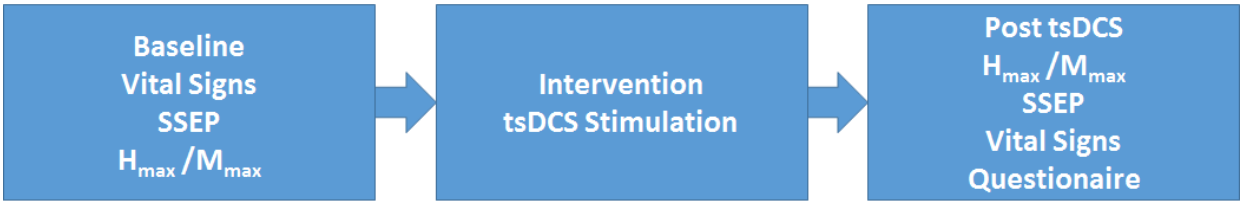

Figure1 : Intervention Visit: Baseline Hmax/Mmax and SSEP will be performed before actual tsDCS intervention. Post

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Baseline: The baseline assessment will be performed on the same visit as intervention and will be performed in the Motor Recovery Laboratory by an evaluator blinded to subject's group assignment.

Vital Signs: Vital signs will be recorded at the beginning of each session.

SSEPs: We will measure SSEPs to evaluate effects of tsDCS on ascending somatosensory pathways. A somatosensory evoked potential (SSEP) is the electrical activity response measured at the skin's surface along ascending sensory pathway following controlled peripheral nerve stimulation. For recording posterior tibial nerve SSEPs, the nerve is stimulated at the ankle, with the cathode midway between the Achilles tendon and the medial malleolus and the anode 3 cm distal to the cathode. Nerve stimulation should consist of a 0.1–0.2 ms duration square wave pulse at 3-5Hz. These pulses will be delivered by constant voltage stimulator applied transcutaneously over the targeted nerve. The stimulation intensity would exceed the motor threshold for eliciting a muscle twitch.[37]We will use same Nihon Kohden clinical EMG/NCV measuring system to measure SSEPs. Procedure will follow per clinical protocol.

Hmax/Mmax ratio: Immediately before and after application of tsDCS we will measure Hmax/Mmax ratio obtained from soleus muscle by stimulation of tibial nerve. The difference between pre and post Hmax/Mmax ratio will be measured. The H-reflex is a compound muscle action potential elicited by low-threshold electrical stimulation of afferent fibers in the mixed nerve with subsequent monosynaptic excitation of alpha motoneurons. Changes in the excitability of the reflex pathway are estimated by measuring the amplitude of the reflex. M wave is a compound muscle action potential produced by direct supra-maximal stimulation of motor axons. The H-reflex amplitude is highly variable, the excitability of the motoneuron pool plays a substantial role in determining the amplitude of the H-reflex. Therefore, changes in the ratio of maximal H-reflex amplitude and maximal M-wave amplitude (Hmax/Mmax) provide a rough estimate of modulation in spinal excitability.[18, 19, 22] It is necessary to normalize this value so between-subject comparisons can be made. These amplitude variations can result from variations in skin resistance, different amounts of subcutaneous fat, and locations of the nerve relative to the stimulus, among others. The most advocated method of H-reflex normalization is eliciting the H-reflex at a percentage of the Mmax. This method entails finding the amplitude of the Mmax and then adjusting the stimulation intensity to produce an H-reflex with amplitude equal to some percentage of the Mmax amplitude.[36]

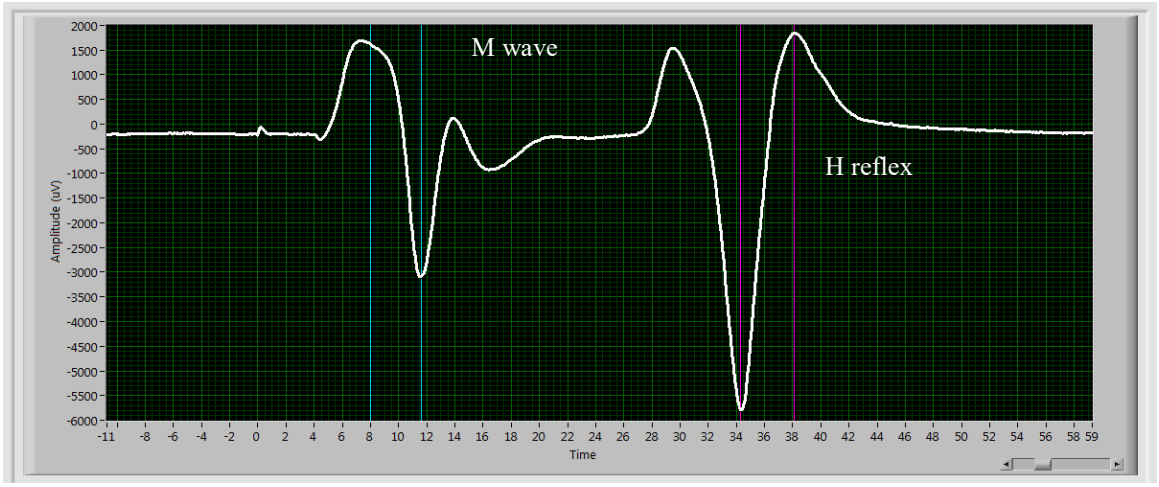

Figure 2: M wave and Hreflex

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tsDCS Stimulation: Spinal stimulation direct current will be delivered by a battery-driven direct current stimulator (Soterix Medical, Model 0707-A) connected to a pair of saline-soaked sponge electrodes Each subject will receive five tsDCS conditions at T10-T11 spinal level with a wash-out period of 1 week between 2 cathodal, 2 anodal and 1 sham tsDCS in a random order. Saline soaked sponge electrodes (36 cm2) will be used to deliver active tsDCS over skin at specified level. Reference electrode will be placed over left shoulder. Active tsDCS (i.e., anodal or cathodal; not sham) will consist of stimulation at an intensity of 2.5 mA for the entirety of each stimulation session (i.e., 2.5mA for 15 minutes to result in a current density of 0.071mA/cm2 and a total delivered charge of 0.064C/cm2). This current density was proven to be safe and sufficient to induce physiological changes in previous human studies.[17, 19, 35] In a study done on healthy subjects (Korupolu PI), current densities above this range resulted in skin blisters. For sham tsDCS, we will start at 0mA and ramp the intensity up, then down, over a 30-second window. This protocol has proven effectiveness for blinding subjects in studies applying direct current stimulation. Figure 3 shows the study design.

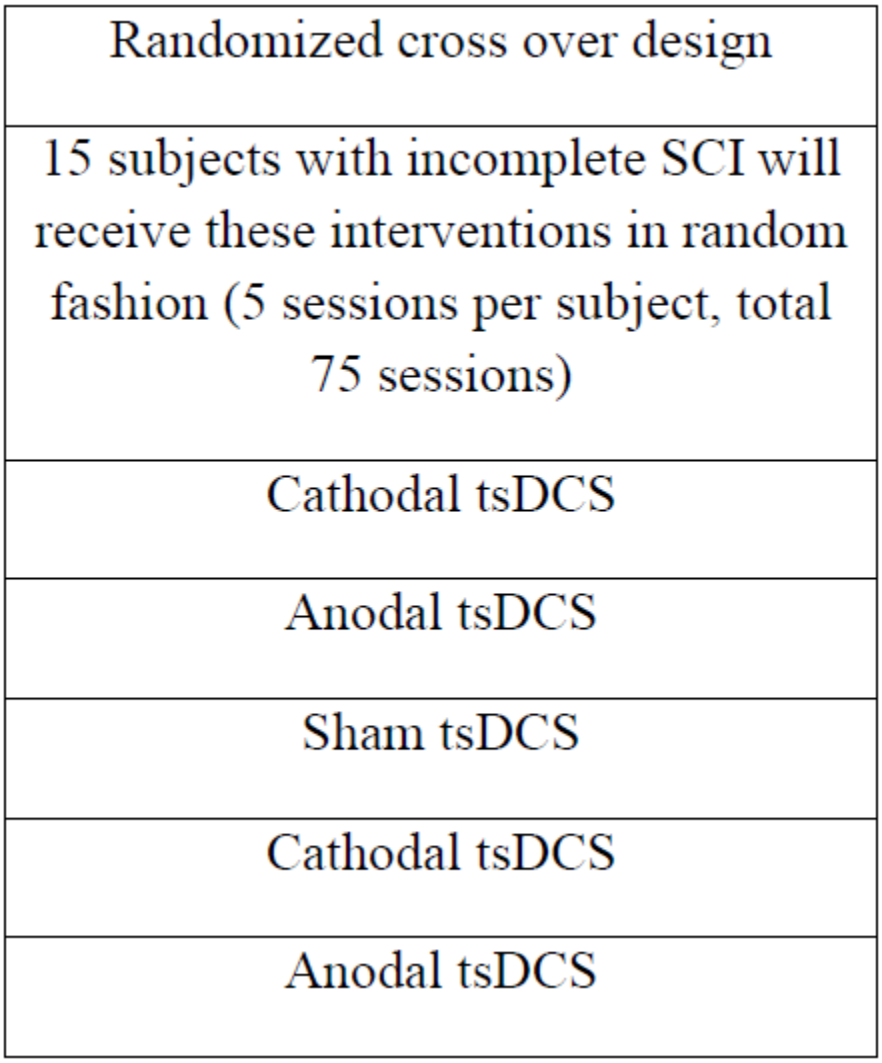

Figure 3 Study Design:Randomization

Post tsDCS: Hmax/Mmax ratio, SSEP and vital signs will be recorded. Similar procedures will be followed as pre intervention assessments for Hmax/Mmax ratio, SSEP and vital signs recordings.

Adverse events: Any adverse events during intervention and collection of pre and post intervention outcomes assessments will be collected.

Assessment	Screening	Intervention 1 (Anodal or Cathodal or Sham)	Washout	Intervention 2 (Anodal or Cathodal or Sham)	Washout	Intervention 3 (Anodal or Cathodal or Sham)	Washout	Intervention 4 (Anodal or Cathodal or Sham)	Washout	Intervention 5 (Anodal or Cathodal or Sham)
	0-30 days prior	Session1	atleast 8 days	Session 2	atleast 8 days	Session 3	atleast 8 days	Session4	atleast 8 days	Session5
ICF	X									
I/E Criteria	X									
Randomization	X									
Demographics	X									
Medical History	X									
Modified Ashworth Scale	X									
Baseline Vital Signs		X		X		X		X		X
Baseline SSEP		X		X		X		X		X
Baseline Hmax/Mmax		X		X		X		X		X
tsDCS		X		X		X		X		X
Post SSEP		X		X		X		X		X
Post Hmax/Mmax		X		X		X		X		X
Post Vital Signs		X		X		X		X		X
Questionnaire		X		X		X		X		X
Adverse Events		X		X		X		X		X

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Table 1: Schedule of visits for SCI participant.

5. SUBJECT POPULATION:

Fifteen adults with SCI will be recruited from TIRR Memorial Hermann, TIRR Outpatient Rehabilitation at Kirby Glen and from the Houston area.

Inclusion Criteria:

1. Providing written informed consent prior to any study related procedures;
2. 18-65 years of age;
3. Motor incomplete SCI classified as B, C or D by the American Spinal Injury Association Impairment Scale (AIS);
4. Traumatic lesion at or above T8-T9 neurological level
5. Body mass index ≤ 30 (in order to facilitate reliable location of body landmarks guiding stimulation);
6. Chronic SCI (time since injury>6 months)

Exclusion Criteria: Subjects will be excluded if they have following conditions

1. Unstable cardiopulmonary conditions;
2. History of seizure, head injury with loss of consciousness, severe alcohol or drug abuse, and/or psychiatric illness;
3. Any joint contracture or severe spasticity, as measured by a Modified Ashworth Score 4;
4. Subject who cannot provide self-transportation to the study location;
5. Cardiac or neural pacemakers;
6. Pregnancy
7. h/o lower motor neuron injury (eg: peripheral neuropathy, cauda equina syndrome)
8. Uncontrolled diabetes with HbA1C>7;
9. History of severe autonomic dysreflexia;
10. alteration in therapy or medication for muscle tone during the course of the study(botulinum toxin injections in last 3 months, phenol injections in last 6 months, intrathecal baclofen pump dose stable for past 3 months, etc);
11. Conditions for e.g., severe arthritis, extreme shoulder pain that would interfere with valid administration of the measures or with interpreting motor testing;
12. contraindications to tsDCS:

- ferromagnetic material in the brain or in the spine (except for titanium used in segmental 9

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fixation of the spine)
- implanted brain medical devices

6. SUBJECT ENROLLMENT:

Potential subjects will be identified by the following sources:

1- Flyers will be posted in the TIRR Memorial Hermann outpatient clinic, TIRR Memorial Herman Adult and Pediatric Outpatient Rehabilitation Kirby Glen, MHH Rehabilitation Centers. Attending physicians and therapists may refer their acquired brain injury outpatients to the study. In order to reach out to individuals with SCI; flyers will be distributed through an e-mail distribution.
2- After subjects are identified by their treating physicians and therapists, they will be referred to the co-investigator. During this first contact, the researcher will briefly explain the study content and request their phone number and e-mail address to contact them later for a pre-screening. During a phone call, a brief pre-screening procedure will be followed. Demographics and medical information such as surgery implants, medications, psychiatric, drug and alcohol history as inclusion and exclusion criteria will be gathered. Dr. Korupolu will review the information gathered during phone screening and may request screening.
3- Potential subjects will be invited to come for a screening visit to Motor Recovery Laboratory at TIRR Memorial Hermann. Any information gathered during phone screening will be stored in a locked file cabinet and password protected electronic file. During the screening visit, an investigator at TIRR will obtain informed consent. The test procedures will be described and the testing equipment will be shown to the subject. Investigator will clearly explain all the procedures and risks of the testing outlined in the consent form. The subject will be given sufficient time to consider their decision and will be encouraged to ask questions, both during the initial interview and throughout the study. The PI or a co-investigator will answer any questions regarding the study at the time consent is given. Once enrolled, the subject may pause or terminate his/her participation at any time during the study.
4- Alternatively any person with SCI who are living in the community and been informed through flyers can contact the researchers directly and request more information about the study.

7. DATA ANALYSIS:

Data analysis: Descriptive statistics will be calculated for all variables. Group analysis of intervention-related changes with fixed effects comparison of post-intervention versus baseline will be performed. We will use repeated measures analysis of covariance to estimate the effect

of group on outcome measures. Stata 14 software will be used to perform analysis. PI has training to use stata software to perform above analysis.

A sample size of 15 subjects was determined based on the review of current literature to determine the optimal polarity for future studies.[17, 19, 22, 35] In these studies 10-12 healthy subjects were evaluated who received one anodal tsDCS, one cathodal tsDCS and sham (total 3 sessions) in cross over fashion. In our study, we plan to deliver 2 cathodal, 2 anodal and one sham session to each subject to improve the strength of the findings. We will have total 75 sessions and 150 data points (pre and post tsDCS outcome assessment) for each outcome measure. This study will provide a strong neurophysiological data for the implementation of future clinical randomized controlled trial studies to evaluate the effects of tsDCS combined with rehabilitation therapy.

8. POTENTIAL RISKS/DISCOMFORTS:

tsDCS: Transcutaneous Spinal Direct Current Stimulation (tsDCS) is a noninvasive procedure in which a device sends a small Direct Current (DC) across the skin to modulate spinal function. The use of tsDCS in therapeutic protocols to date has not resulted in severe adverse effects. In addition our protocol of 2.5mA has been used by other researchers with no signficant adverse events

SSEP: Somatosensory evoked potential is recording electrical signals of sensation going from body to brain. Recording electrodes are attached to the scalp and arm. The stimulus will last about 2 minutes at a time and may cause some twitching and tingling sensation in the target area. However it is painless and carries no significant risk.

Spinal reflexes measurement: Stimuli above the action threshold of peripheral nerves will be administered through skin. This might cause some discomfort that is anticipated to be mild and easily tolerated by the subjects. Also skin irritation might occur due to electrode attachment to the skin.

Assessment/Questionnaires: All assessments will be performed in a designated room inside Motor Recovery Laboratory. None of these tests are either painful or uncomfortable to perform. In order to prevent potential embarrassment during the testing the test will be done individually and in private. If subjects feel uncomfortable in answering any of the questions they may stop the study at anytime.

9. POTENTIAL BENEFITS:

As with any study focusing on basic research, the subjects will derive no direct benefit. The results of these studies may benefit subsequent future subjects. We envision that in the near future the information obtained from the proposed research will provide a better understanding

for treatment options of SCI population.

10. RISK-BENEFIT RATIO:

The potential improvement of arm and hand movement outweighs the risk of non-invasive spine stimulation, fatigue, pain and discomfort.

11. CONSENT PROCEDURES:

Informed consent will be obtained from the subject at Motor Recovery Laboratory at The Institute for Rehabilitation and Research. After the patient is identified by the PI and her research team study criteria and he/she is interested in participating, informed, written consent will be obtained by a member of the research team.

In addition a photography/videotaping consent will be obtained from the subject, if he/she agrees to be photographed / videotaped during the assessments or treatment sessions.

12. CONFIDENTIALITY PROCEDURE:

All data will be coded with identification number, database will be in a password –protected computer and kept in a locked file cabinet.

13. COSTS

The subject will not be expected to pay any costs.

14. PAYMENTS:

Subject receive up to $75 to help cover the cost of transportation and parking if they attend all five of your scheduled sessions.

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