IRB Study Number:20200090
Version #, Date: 07/13/2023

1) Protocol Title

- **Title of Study**: Balance Training with Transcranial Direct Current Stimulation for Chronic Ankle Instability
- **eProst ID** Number: 20200090
- **Version** Number: 1
- **Version Data**: 07/13/2023
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- **National Clinical Trial Number**: NCT04390048.

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2) Objectives*

The purpose of this study is to investigate the effect of balance training with transcranial direct current stimulation (tDCS) on postural balance, self-reported functions, and neural functions in individuals with chronic ankle instability (CAI).

3) Background*

Ankle sprain is the most common injury in physically active individuals.[1] A significant proportion of ankle sprain patients suffer from residual symptoms and recurrent injuries, and develop a chronic disease, clinically termed as chronic ankle instability (CAI).[2-4] CAI is a multifactorial condition involving a variety of predisposing factors for CAI: muscle weakness [5], muscle activation failure [6], postural control impairments [7], and altered joint mechanics [8-9]. However, among these factors, it is well known that postural control plays an essential role in ankle instability. For this reason, discovering the underlying mechanisms of impaired postural control has been a primary focus in the CAI literature. With recent advances in neurophysiological technology, sport medicine researchers have begun to examine specific mechanisms regarding impaired postural control following ankle injuries. Recent studies [10-16] have demonstrated altered neural functions in CAI patients. Patients with CAI demonstrated deficits in spinal excitability [11, 14], cortical excitability [10, 12, 14, 15], smaller excitable cortical areas of lower leg muscle [17], and higher fluctuations of cortical activation [13] compared to healthy individuals. These findings [10-16] indicate the alteration of neural functions in patients with CAI, which may be related with postural control deficit, and clearly suggest a new therapeutic target, not just treating the ankle joint, but the brain control in CAI patients.

Balance training (BT) has been frequently used by clinicians for improving postural control in CAI patients.[18-21] However, recent research with advanced analysis techniques for postural control found that the current BT may not be ideal, as only one third of CAI patients presented clinically meaningful improvements.[22] Besides, BT was not strong enough to restore the decreased cortical activation [23] that is potentially linked to poor postural control in CAI patients. These results [22, 23] suggest that the need for potential adjunctive rehabilitation that is capable of altering the ongoing maladaptive brain plasticity in order to supplement the clinical efficacy of BT for CAI patients.

Transcranial direct current stimulation (tDCS) is an non-invasive electrical stimulation technique over the brain that safely influences the cortical excitability, and it is a painless and portable.[24-29] It is thought that a subtle electrical current (up to 2.0 mA) can induce facilitatory effects on cortical excitability of the primary motor cortex: The anodal (+) stimulation is known to increase cortical excitability while cathodal (-) stimulation decreases the excitability.[31-33] Given these positive outcomes and high applicability (safe, portable, and easy-to-use), tDCS has been extensively used in the neuroscience literature[34-38] to address neurological symptoms including impaired postural control and motor dysfunction in a wide range

of neurological patients such as stroke[38], Parkinson's disease[36], and spinal cord injury[37].

There are emerging interests in tDCS to address musculoskeletal conditions. A recent study [39] has examined its efficacy for patients with chronic low back pain and confirmed its effects on pain and postural control. Anodal tDCS was applied to the motor cortex area during 20 minutes of balance training: It was found that pain and postural control were significantly improved after the intervention (tDCS with balance training).[39] Besides, tDCS has been used in patients with CAI. The tDCS was applied to the patients before they began their strength training. The use of tDCS in combination with strength training was found superior to strength training alone CAI patients.[40] This tDCS study for CAI clearly shows that CAI patients are responsive, and raise the potential that tDCS can be incorporated into other CAI rehabilitation programs such as balance training. Thus, it is possible to hypothesize that BT with tDCS would improve postural control and patients reported outcome along with enhancement in neural excitability, which induces superior improvements to BT alone.

4) Inclusion and Exclusion Criteria*

Below are characteristics of the subject population

- Anticipated number: 60 human subjects with chronic ankle instability
- Age: 18-45
- Sex: Both
- Race: All

Criteria for inclusion:

- Subjects should be neurologically sound.
- Subjects should have abilities to maintain single leg stance at least for 10 seconds.
- A history of ankle sprain
- A history of ankle joint giving ways
- Current feelings of ankle joint instability

Criteria for exclusion:

- Individuals with a clinically defined neurological disorder, with an increased risk of seizure for any reason, with a history of treatment with TMS, deep brain stimulation for any disorder will be excluded.
- Patients with cardiac pacemakers, implanted medication pumps, intracardiac lines, or acute, unstable cardiac disease, with intracranial implants (e.g. aneurysm clips, shunts, stimulators, cochlear implants, or electrodes) or any other metal object within or near the head, excluding the mouth, that cannot be safely removed will be excluded.
- A history of balance or vestibular disorder
- A history of previous surgeries to the musculoskeletal structures in either limb of the lower extremity
- A history of a fracture in either limb of the lower extremity requiring realignment

- A history of acute injuries to the lower extremity joints in the previous 3 months, which impacted joint integrity and function (i.e., sprains, fractures) resulting in at least 1 interrupted day of desired physical activity
- A history of herniated disc
- Poorly controlled headache
- Hypersensitivity to electrical or magnetic stimulation

The study will not recruit any of the special classes of subjects as shown below.

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

5) Procedures Involved*

Study Overview

The proposed study is a double-blinded, randomized-control design which examines the efficacy of tDCS with balance training (BT) for patients with chronic ankle instability (CAI). Participants will be randomly allocated to one of two groups including (1) anodal tDCS + BT and (2) sham tDCS + BT. Outcome measures allow us to measure effects on postural balance, neural functions, and self-reported physical function.

General Procedures

Figure 1 illustrates the study flow, procedures and design. Participants will undergo brief screening over the phone or email to ensure they meet inclusion criteria. A face-to-face baseline assessment will be scheduled for eligible individuals at the Sports Medicine Laboratory in the Max Orovitz Building. Potential participants will be given a full description of the study procedures and asked to read and sign an IRB-approved informed consent form before any study procedures or assessments are conducted. Consent will take place in a private office and will be conducted by trained staff, including the principal investigator, co-investigator, research assistant. All participants who provide written consents will be screened for their current health status to determine whether they qualify for participating in the study. The screening involves several questionnaires to be administered by a certified athletic trainer to ensure eligibilities and safety of participants (Appendices A-C). For qualified participants, the certified clinician will perform a standard physical exam of the ankle joint and quantify a current level of physical activity using physical activity questionnaire (Appendix D-E). During the preintervention measurement, eligible participants will complete a battery of assessments including postural control, self-reported functions, and neural functions.

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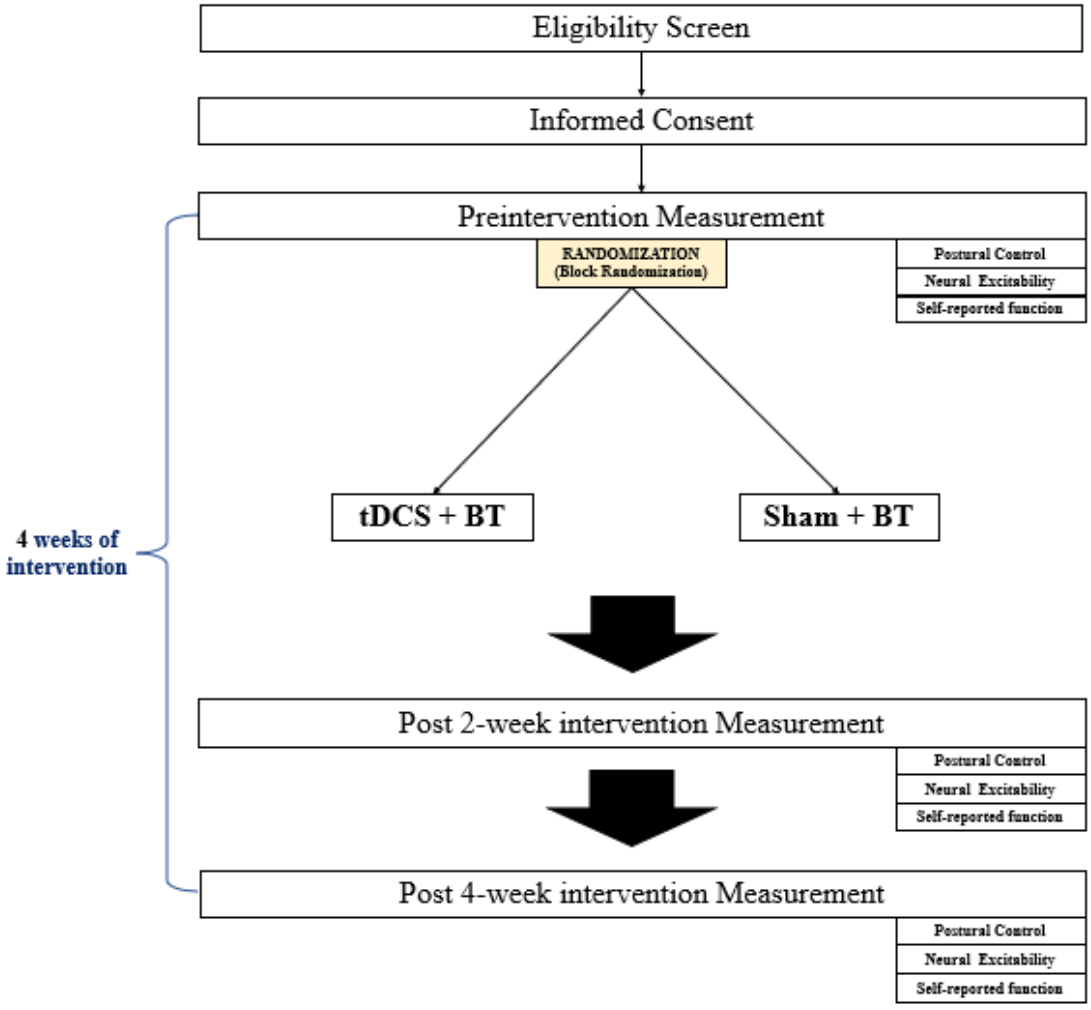

Figure 1. Flowchart of Overall Study Design and Procedure

There will be one screening day and 2 separate testing days (Figure 2). On the screening day, participants will fill out the CAIT and health questionnaire to determine the presence of CAI. On the first testing day, self-reported function (FAAM), static postural control, and neural excitability (H-reflex, TMS) will be measured. On the second testing day, dynamic postural control (SEBT and side hop) will be measured. The testing days will be separated by at least 24 hours (Figure 2). The testing will repeat at post-2-weeks and post 4-weeks of intervention measurement.

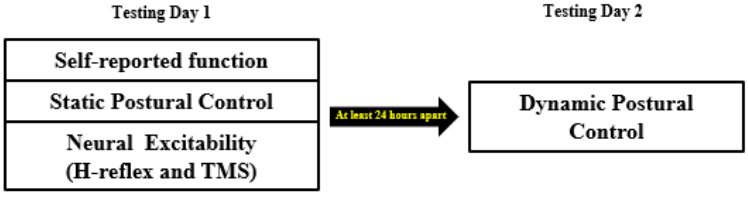

Figure 2. Outcome measures at testing day 1 and 2.

The first testing day: Once participants arrive at the lab, they will complete health questionnaire, including the Foot and Ankle Ability Measures (FAAM). Then, they will be asked to do 5~10 minutes of a warm-up. After the warm-up, the investigator will assess double leg balance and a single-leg balance. The static postural control testing requires 3 successful trials of balance for each task. During the static postural control assessment, concomitant assessments of ankle muscle activation (soleus, fibularis longus, and tibialis anterior) will be assessed. Once a participant finishes the static postural control assessment, neural excitability testing will be performed in the counterbalanced order of TMS and H-reflex to prevent the order effect.
The second testing day: Once participants arrive at the lab, they will be asked to do the warm-up. After the warm-up, participants will perform dynamic postural control tests (star excursion balance test and side hop). The detailed procedures for each outcome measure are described in the following subsections.

Outcome Measures

Spinal Excitability (H-reflex): The cathode (2 mm shield disk electrode, BIOPAC Systems Inc., Goleta CA, USA) will be secured over in the superior popliteal fossa proximal to the bifurcation the tibial and common peroneal nerve with a strip of hypoallergenic tape and the dispersive electrode (circular carbon-impregnated dispersive pad) will be positioned on the anterior thigh just above the patella. The soleus H-reflex will be elicited by a 1-ms square-wave electrical stimulus applied to the sciatic nerve at increasing intensities until a maximal Hoffmann reflex (H-reflex) and maximal motor response (M-response) are found. The soleus muscle was selected due to its functional role in postural control. Five maximal H-reflex and M-response measurements will be recorded. The averages of both responses will be used to calculate the Hmax/Mmax ratio as an outcome variable representing the spinal excitability. **Corticospinal Excitability (TMS):** The participant will be accustomed to the stimulus by progressively increasing the TMS stimulator (Magstim Company Ltd, Wales, UK) intensity up to the intensity that results in motor response. The participant may feel minimal sensations at the point of application (like a puff of air on the scalp). After a brief introduction of the stimulation, participants will be asked to wear a Lycra swim cap that has a dot grid line (1cm x 1cm squares) and a straight line in the middle sagittal plane in order to navigate the brain area. A series of TMS stimuli of 1.0 Tesla will be delivered to identify the location of the motor cortex where the investigator observes the largest amplitude (hotspot). Once the hotspot is determined, a magnetic field will be introduced to the scalp at a location in the primary motor cortex where cortical neurons innervating the soleus muscle are located. When the magnetic field is received at the primary motor cortex at the appropriate area, motor signals are sent to the soleus muscle. We will record these signals with surface electrodes that are on the soleus muscle. As the intensity of the TMS increases, the soleus muscle will briefly contract/twitch that is known as motor-evoked potential (MEP). The contraction is comparable to what would be felt during standard medical reflex testing. The active motor threshold (AMT) will be defined as the stimulator intensity required to elicit a peak-to-peak MEP amplitude above 3 standard deviations of mean soleus EMG activity during10-sec of both single and double leg stance. AMT will be determined by using a software that runs the

maximum-likelihood threshold tracking algorithm, Parameter Estimation by Sequential Testing (PEST). Ten trials of TMS will be delivered at two different TMS intensities of AMT110% and 120% in order to assess motor neuron activity at the supra-spinal level. TMS tests will be performed while participants maintain single and double leg balance. The averages of responses at each intensity will be used as an outcome variable representing the corticospinal excitability. **Electromyography (EMG):** For measurements of H-reflex and TMS responses, it requires EMG signals from muscles to be recorded. A total of 4 EMG Ag-AgCl electrodes will be placed over the lower leg muscles including soleus, fibularis longus, and tibialis anterior and the one reference electrode on the lateral malleolus. The surface EMG electrode will be placed based on the SENIAM recommendations. **Static Postural Control:** The static postural control will be measured at unipedal and bipedal stance on a force plate (Accusway Plus, AMTI, Waterfront, MA). For bipedal stance, participants will be asked to maintain a barefoot stance with their shoulder-width apart and crossed arms on the chest. The foot positions will be outlined with tape. Participants will be asked to stand as still as possible during testing. Participants will complete three trials of bipedal stance with eyes open and eyes closed condition for 10 seconds each trial. After the bipedal balance testing, the participant will be asked to perform unipedal balance testing. Participants will be asked to stand on their involved limbs of CAI. The stance foot will be put on the midlines of the forceplate. The participant will be asked to maintain their unipedal stance. Participants will complete three trials of unipedal stance with eyes open and eyes closed condition for 10 seconds each trial. If a participant touches down with the opposite limb, contacts the stance limb, or is unable to maintain standing posture during the 10-second trial, the trial would be terminated and repeated. Successful trials of each balance testing will be recorded. **Dynamic Postural Control**: **Star Excursion Balance Test (SEBT):** SEBT is a clinical assessment for functional deficits of lower extremity balance. Participants will be asked to stand barefoot on a firm surface. Participants will stand on a single leg with the CAI involved limb placed at the center of different lines (anterior (A), posteromedial (PM), postero-lateral (PL). Participants will be asked to reach the furthest point on the line with extending their contralateral foot. Participants will be asked not to move their stance foot from their center position, with hands on the hip. The distance from the center of the grid to the furthest reach point will be manually measured in cm with a measuring tape. Three testing trials with 4 practice trials will be performed with each participant in each direction on each side. The mean of three trials will be used for the analysis. **Side Hop:** All participants will be instructed to hop on their CAI-involved limbs. Participants will be instructed to hop laterally over a 30-cm distance by alternating sides from lateral direction back to the starting location with an involved limb. One repetition will be the ability to hop laterally and return to the starting location. Participants will be instructed to complete 10 repetitions as quickly as possible. Testing trials will be repeated until 3 successful ones. If a participant falls, put the contralateral foot on the ground, and do not follow the course outline, the trial will be considered “a failed trial.” The examiner will record the total time to complete the trial, using the stopwatch, to the nearest 0.01 second. Participants will perform three practice trials, followed by 3 testing trials. The average of 3 testing trials will be recorded and used for analysis. **Self-reported**

functions: The Foot and Ankle Ability Measure (FAAM) is a self-reported measurement designed to examine ankle function for patients with foot and ankle related impairments. FAAM is divided into two subscales, such as Activities of Daily Living (ADL) and Sports Subscale. The FAAM-ADL consists of 21-item questionnaire and assesses various ankle activities such as standing, walking, stepping, and squatting. The FAAM-Sports consist of 8-items questionnaire and assess more challenging activities related to sport such as running, jumping, landing, starting-stopping quickly, cutting movements and sports specific movement. Both FAMM-ADL and Sports will be administered to each of participants. The investigator will guide participants how to fill out the ankle questionnaire. Once participants complete the questionnaire, the investigator will score each questionnaire. Each item is scored on a 5-point scale from "no difficulty at all" being 4 points to "unable to do" being 0 points. The total score for FAAM-ADL is 84, and FAAM-Sport is 32, which will be transformed into percentage scores. A higher percentage represents higher levels of ankle function. These percentage scores provide perceived ankle dysfunction in patients with CAI. The FAAM is a reliable and valid measure for patients with CAI.

Study Interventions

Transcranial Direct Current Stimulation: Participants in the active and sham tDCS groups will receive tDCS while performing balance exercises (about 20-min application). An anodal surface electrode will be attached to the contralateral motor cortex (M1) of the CAI-involved side and the reference electrode will be placed on the ipsilateral side of the supraorbital ridge. These electrode placements (stimulation sites) were consistent with previous studies.[39, 40] Anodal tDCS will deliver a low electrical current stimulation at 2 mA, while for sham tDCS, the stimulator will be turned off automatically 30 s following the application. The sham stimulation mimics the transient scalp sensation perceived when the stimulator is initially switched on. This technique is currently state-of-the-art for conducting convincing sham stimulation in the tDCS field. For tDCS treatment set-up, participants will sit on the chair. Sponge electrodes will be placed and secured with a head strap: Active electrode over the motor cortex area and the reference electrode on the contralateral side of the upper forehead. The tDCS set-up will take approximately 10 minutes. Participants will undergo 12 sessions (20-min each) of active or sham tDCS using 2mA current. This constant current device ramps up to the desired amplitude and ramps the amplitude back to 0mA at the end of the treatment duration. tDCS (real or sham) will be delivered from beginning of balance training to the end of the training. After each training session, an aloe cream will be applied to the skin under the electrodes to reduce risks associated with skin drying. **Balance training:** All groups will receive the same progressive balance training (BT). BT will be implemented 3 times a week over 4 weeks, each training session lasting about 20 minutes. The 4 weeks of BT has been shown effective in enhancing postural control in patients with CAI. The BT will consist of 3 types of balance exercises: (A) single-leg stance exercise with eyes open and closed and on stable and unstable surfaces, (B) single-leg deadlift exercise with eyes open and on stable and unstable surface, and (C) balance

exercise on wobble board. Participants will be asked to perform a progressive level of exercise in each session.
The single-leg exercise is static balance exercise. Participants will be instructed to maintain their single leg balance with their CAI involved limb as still as possible. There will be 6 levels of difficulty. Participants will advance to the next level if they demonstrate error-free performance. The error includes falling, touching down with the opposite limb, bracing the non-stance limb against the stance limb, and opening the eyes during the eyes-closed condition.
Single leg deadlift is a semi-dynamic balance exercise that involves a hip-hinge movement while maintaining a single-leg balance. Participants will be instructed to stand with their feet hip-width apart and parallel, Then, they will be asked to lean forward in their torso by shifting the weight onto the involved leg while the non-weight bearing leg extends backward. The extended leg will be lifted, and the torso will be shifted forward until the "T" shape is formed. There will be 6 levels of difficulty. Participants will advance to the next level if they perform the deadlift without errors including excessive trunk motion (more than 30 degrees of lateral flexion), removing the hands from the hips for the related activities, and missing the target.
The wobble board exercise is a dynamic balance exercise. The wobble board is a circular plate (30 inches) with different sides of domes that screw into the bottom of the board to make balance exercises challenging. Participants will perform the exercise near a wall and be only allowed to touch fingertips to the wall for stability. A balance exercise will be performed on the board, and then clockwise and counterclockwise rotations of the rim of the board will be completed. The dome with the shortest diameter will be considered the lowest level (e.g., level 1) and all participants will begin performance on this level. Five levels will be used for training, and height of each level increased by half inches. Thus, heights ranged between 1 and 3 inches. The initial direction of rotation will be selected by participants and will be changed every 10 seconds of the 40-second trial. There will be 5 difficulty levels. Participants will be progressed to the next level if they perform balance on the board with smooth transitions between and within rotation directions as well as self-reported feelings of "easiness.

6) Data and Specimen Banking*

All data collected from this study will be stored on password protected computers at the Sports Medicine Laboratory in the Max Orovitz Building. Participants will be assigned own identification number at the time of participation. Our laboratory is in a locked building with limited key card swipe access. Only investigators for this study will have access to the data.

7) Data Management*

Data will be stored in a personal computer which is in locked research offices and is encrypted and password protected. The means and standard deviations will be calculated for one pre and two post outcome measures and will be used for statistical analysis. The normal distribution of data will be assessed by using the Shapiro-Wilk tests. For each outcome measures (postural control, neural measures, and self-

reported function), 2 (group: anodal tDCS+BT and sham tDCS+BT) by 3 (time: pre-intervention, 2 weeks post-, 4 weeks post-intervention) ANOVA with repeated measures will be performed to determine effects of tDCS for each outcome measure. In the presence of a significant group-by-time interaction, a post-hoc analysis using Sidak adjustment will be conducted. The level of significance will be set a priori at 0.05. All statistical analyses will be performed using SPSS 26.0 statistical software (SPSS Incorporated, Chicago, IL, USA).

8) Risks to Subjects*

tDCS risks and safety plan

The risks associated with tDCS are minimal. There is no documented risk of seizure associated with tDCS, but participants with a history of seizure disorder will be excluded to ensure optimum safety. Side effects associated with tDCS include mild headache, tingling, itching, or stinging under the electrodes, and skin irritation. After each therapy session, an aloe cream will be applied to the skin under the electrodes to reduce risks associated with skin drying.

Balance training and safety plan

There is a small risk that balance training cause injury during balance training, but participants may feel mild muscle soreness during and after balance training activities. For the safety of participants, all exercise sessions will be supervised by a certified athletic trainer. If participants perform an activity in a way that may hurt them, they can take a rest anytime they want, and we will demonstrate a proper form of exercise.

TMS risks and safety plan

TMS is a safe procedure that has been used on many people to study the brain. Most people do not find the stimulation painful, but occasionally strong contractions of scalp muscles can cause some discomfort or headache. TMS-induced headaches are mild and brief (less than 1 hour).

If a headache or mild scalp discomfort occurs, subjects will be directed to use over the counter pain medication at their own discretion. The symptoms usually go away promptly with nonprescription medication.

The noise of the TMS magnet may affect hearing, so subjects will be required to wear disposable earplugs during TMS session.

The risk of inducing a seizure with single-pulse TMS* is considered very low. Seizures from single-pulse TMS have only been reported in subjects with medically-intractable epilepsy very rarely (0.0-3%).

In the unlikely event of a seizure, a standard seizure protocol will be followed.

1. First thing: REMOVE THE COIL FROM SUBJECT'S BRAIN
2. Remove harmful objects from the subject's surrounding area
3. Cushion the head as possible and the area so subject does not injure themselves
4. If the subject is having trouble breathing, turn the subject on their side
5. Monitor the duration of the seizure
6. If the seizure ends in less than 60 seconds, monitor and contact primary care doctor to rule out predisposing factors

7. If seizure lasts more than 60 seconds, activate emergency services.

Precautions:
Do not place anything or any fingers anywhere near the mouth
Do not attempt to hold the subject down
Remain calm, seizures almost always stop after a few minutes

TMS can interfere with implanted medical devices and will not be done in people who have pacemakers, implanted pumps, or stimulators, such as cochlear implants or in people who have metal objects inside the eye or skull. All participants will be screened before enrollment to assure that they meet study criteria and that there are no contraindications to TMS, subjects will be instructed that they can discontinue the TMS experiment at any time
* The amount of energy introduced to the body is considered safe. The duration of the stimulus is extremely brief (less than 1 millisecond) and the maximum intensity is 1.4 Tesla (less than magnetic resonance imaging). The magnetic stimulation in this study feels similar to a gentle tap on the head. Please note the proposed study will utilize the single-pulse TMS that has been considered safer than other types of TMS techniques such as paired-pulse or repetitive TMS. FDA has approved repetitive TMS to treat depression.

H-reflex and M-response risks and safety plan

H-reflex and M-response are also considered a safe procedure that has been used on many people to study the peripheral nerves. Most people do not find the stimulation painful, but occasionally strong contractions of tested muscles can cause some discomfort or pain. Stimulation-induced pain is mild and short (less than 4 hours). The pain is usually manageable with nonprescription pain medication.
** The amount of energy introduced to the body is not significant. The duration of the stimulus is extremely brief (1 millisecond) and the maximum intensity is 200V. The shocks in this study feel like a shock of static electricity, like when you are walking across a carpet and then touch a door knob, except the voltage is much lower (A shock of static electricity can provide up to thousands of volts of electricity).

9) Potential Benefits to Subjects*

There will be no guarantee of a specific benefit to individual participants; however, successful completion of this study will open a new class of therapeutic approaches for individuals with chronic ankle instability.

10) Vulnerable Populations*

N/A

11) Setting

Data collection will take place at the Sports Medicine and Motion Analysis Laboratory at University of Miami.

12) Resources Available

All necessary equipment is available in the Sports Medicine and Motion Analysis Laboratory, and the investigators have considerable experience to safely conduct the proposed study.

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13) Prior Approvals

This project has been approved by the Department of Kinesiology and Sports Sciences in the School of Education as a dissertation research project.

14) Recruitment Methods

Subjects will be recruited from the University of Miami's Medical and Coral Gables campuses as well as community centers and local sports medicine and orthopedic clinics. Flyers and emails approved by the University of Miami's Institutional Review Board (IRB) for the Use and Protection of Human Subjects will be used when permitted. We will be seeking permission to send an email to potential people by identifying in-charge person/officer in each university unit (i.e., departments, club sports teams, athletics) or building, who can provide us with a list of email addresses or can send an email for us. We will do the same for other places outside the university community.

15) Local Number of Subjects

Sixty human subjects with chronic ankle instability will be recruited and enrolled in the study. A statistical power analysis was performed to estimate sample size, based on the previous tDCS study [40] on CAI patients with similar dependent variables (e.g., corticospinal excitability). The effect size (f=0.55) in this study was large using Cohen's criteria. With an alpha=0.05 and power = 0.80, the projected sample size needed is approximately 8 participants for each group with a total of 24 CAI patients. Thus, the proposed sample size of 20 for each group with a total of 60 CAI patients will be more than adequate and should also allow for expected attrition.

16) Confidentiality

All collected data will be kept in a locked cabinet at the laboratory (Room 123 in the Max Orovitz, 1507 Levante Ave. Coral Gables, FL). Only the principal researcher and his research staff will be allowed access. All electronic data will be stored in a password-locked computer that is kept in the locked cabinet, and only the principal researcher and his research staff will have the password. All records will be identified using only ID numbers and no information than may reveal the subject's identity will be attached to these records. The ID list and the signed consent forms will be kept in a separate locked cabinet in the room 120, only accessible by the principal researcher.

17) Provisions to Protect the Privacy Interests of Subjects

All interactions will be limited to the principal investigator and study team.

18) Consent Process

A signed informed consent form will be required from all subjects participating in the study. The consent form will be in plain language and describe all aspects of the study: the purpose, procedure, time requirements, and any potential risk factors associated with participation. Informed consent will be obtained from subjects upon during the first visit to the lab (University of Miami, Coral Gables). Informed consent will be reviewed by the subject and explained by researcher. This will include answering any questions the subject has. The PI will obtain consent.

19) Process to Document Consent in Writing

Consent form attached

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