IRB Approved Protocol, Consent and Statistical Plan :

Title: Can transcranial direct current stimulation improve ambulation and fatigue resistance in people with MS?

NCT #: NCT02987621

Document date: 08/24/2017

PROTOCOL
Biomedical
Colorado State
University

Protocol # 16-6856H
Date Printed: 07/18/2018

Protocol Title: Can transcranial direct current stimulation improve ambulation and fatigue resistance in people with MS?

Protocol Type: Biomedical

Date Submitted: 08/24/2017

Approval Period: 09/15/2017-09/14/2018

Important Note: This Print View may not reflect all comments and contingencies for approval. Please check the comments section of the online protocol.
Questions that appear to not have been answered may not have been required for this submission. Please see the system application for more details.

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* * * Continuing review * * *

To renew your protocol: 1. Complete this one-page form; 2. If necessary, update any sections of the protocol that need to be updated for the upcoming year (e.g., change in personnel, location); 3. Electronically "sign" the application by clicking in the check box on the bottom of the "Obligations" page; 4. Remember to click "Submit Form" and confirm your intent to submit by clicking "OK" so that the IRB administrators receive your application. You must answer each question. Input N/A to answer any questions that are not applicable. NOTE: Documents that contain much of the information required to answer the participant number questions below can be found in the "Event History" section of each protocol. The status on your homepage will be "Submitted to IRB" when your submission is successful. IMPORTANT: If the Department Head has changed since your last approval, please be sure to update the Department Head listing on the personnel Information screen of your protocol.

1. Summary: Number of Participants Associated with the Protocol:

   a. Total number of participants approved to date:
   40 (20 strength and 20 fatigue)

   b. Number of participants studied since the last approval date:
   5 (1 strength and 4 fatigue)

   c. Total number of participants studied since the beginning of the project:
   5 (1 strength and 4 fatigue)

   d. Number of participants remaining to study (total number of participants approved LESS the total number of participants studied to date):
   35

   e. Please explain if there is a discrepancy in participant numbers (e.g., more participants responded to a survey than had been approved):
   n/a

2. a. Reasons and number of withdrawals from the research (both subject and investigator initiated) since the last approval date.
   none

b. Number of subjects lost to follow-up since the beginning of the study.

none

c. Please summarize any protocol deviations/violations or unanticipated problems (UPs)/adverse events (AEs) since the last continuing review or original approval (if this is your first continuing review). Please indicate if any of the unanticipated problems/events are being reported to the IRB for the first time. If you have or will make changes to your protocol as a result of any unanticipated problem/event or adverse event, please summarize those changes in Question #5 below.

none

e. Complaints about the research during the last year.

none

3. A summary of any recent findings, literature, or other relevant information (especially pertaining to risks), if applicable.

none

4. Description of the remainder of project:

Y Do you plan to recruit more subjects?

If "No," have all subjects completed all research-related interventions? Note: Protocols must be renewed to continue recruiting participants and/or collect data from already recruited participants.

N Are you only performing data analysis? NOTE: If you are analyzing data with no identifiers (i.e., you cannot link your data to individuals), you can close your protocol by submitting a Final Report.

N Does this protocol have a Data Satety Monitoring Board (DSMB)?

If you do have a DSMB, have reports been submitted to the IRB and/or the Sponsor? Upload any DSMB reports that have not yet been submitted to the IRB since the approval or last continuing review.

5. Summarize all approved changes in the protocol since the last continuing review or since the original approval (if this is your first continuing review). For example: Have you amended your protocol during the past year? Are you requesting to make any changes for the upcoming year? Have you included any changes as a result of an unanticipated problem/event or Adverse events (AE)? Have there been any personnel changes in the past year (including a change in department head)?

Amendment 1: Added clinicialtrials.gov language to the consent
Amendment 2: Removed the requirement of physician clearance and updated screener to mimic other tDCS protocol
Amendment 3: Add compensation for fatigue group and the strength group was closed to enrollment. Please note: the investigator would like to keep the strength group open to enrollment, please revise in the next approval letter.

If necessary, proceed to the appropriate section(s) of the protocol and make your requested changes. Remember that if you are requesting to revise a document that is already attached, you must delete the already attached document and upload the revised document.

6. **List of Protocol Sections (and questions) that have been changed/modified.**

Updated Felix Proessl's personnel status

Please note: the investigator would like to keep the strength group open to enrollment, please revise in the approval letter.

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* * * Personnel Information * * *

IMPORTANT NOTE: Mandatory Personnel on a protocol are: Principal Investigator and Department Head. Only the Principal Investigator can submit the protocol; although other personnel listed on the protocol can create the protocol. Human Subjects Protection Training is mandatory for Principal Investigator, Co-Principal Investigator, and Key Personnel (as defined by NIH). Training must be updated every three (3) years.

Principal Investigator Mandatory

Name of Principal Investigator (Faculty, Staff or Postdoc)	Degree	Title
Rudroff, Thorsten		Assistant Professor
Email	**Phone**	**Fax**
Thorsten.Rudroff@colostate.edu	(970) 491-8655	
Department Name	**Campus Delivery Code**	
1582 Dept Hlth & Exer Sci		
Human Subjects Training Completed? PIs must complete training every three (3) years.		Y

CO-Principal Investigator

Name of Co-Principal Investigator (This could be another faculty or a Master's or Ph.D. student)	Degree	Title
Kindred, John		Graduate Assistant
Email	**Phone**	**Fax**
John.Kindred@colostate.edu		
Department Name	**Campus Delivery Code**	
1582 Dept Hlth & Exer Sci		
Human Subjects Training Completed? Training is required for Co-PI. Training must be updated every three (3) years.		Y

No training data is available.

Additional Co-Principal Investigator

Name of Additional Co-Principal Investigator	Degree	Title
Ketelhut, Nathan		Graduate Assistant
Email	**Phone**	**Fax**
Nathan.Ketelhut@colostate.edu		
Department Name	**Campus Delivery Code (CSU) or off-campus mailing address**	
1582 Dept Hlth & Exer Sci		
Human Subjects Training Completed? Training is required for Co-PI. Training must be updated every three (3) years.		Y

Name of Additional Co-Principal Investigator	Degree	Title
Proessl, Felix		Graduate Assistant
Email	**Phone**	**Fax**
Felix.Proessl@colostate.edu		
Department Name	**Campus Delivery Code (CSU) or off-campus mailing address**	
1582 Dept Hlth & Exer Sci		
Human Subjects Training Completed? Training is required for Co-PI. Training must be updated every three (3) years.		Y

Department Head Mandatory

Name of Department Head	Degree	Title
Braun, Barry		Professor
Email	**Phone**	**Fax**
Barry.Braun@colostate.edu	(970) 491-7875	
Department Name	**Campus Delivery Code**	
1582 Dept Hlth & Exer Sci		
Human Subjects Training Completed?? Training is not required for Department Head. Select "No" if you do not know if your Department Head has completed training or not.		Y

Administrative Contact

Name of Administrative Contact, Project Director, or Lab Coordinator	Degree:	Title
Biela, Laurie		
Email	**Phone**	**Fax**
Laurie.Biela@colostate.edu		
Department Name	**Campus Delivery Code**	
1582 Dept Hlth & Exer Sci		
Human Subjects Training Completed? Training is not required for Administrative Contacts		Y

No training data is available.

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* * * Subject Population * * *

Subject Population(s) Checklist

Â Select All That Apply - Note that this is your Targeted Population :

X Adult Volunteers
Decisionally Challenged
Elderly
Employees
Fetuses

X Long-Term Patients
Mentally Disabled
Minors (under 18)
Pregnant Women
Prisoners
Soldiers
Students
Other (i.e., non-English Speaking or any population that is not specified above)

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* * * Study Location * * *

Study Location(s) Checklist

Select All That Apply - NOTE: Check "Other" and input text: 1.) If your study location is not listed, or 2.) If you would like to list details of your already-checked location (e.g., specific school within a school district)

Aims Community College
Colorado Department of Public Health & Environment
X Colorado State University
Colorado State University - Pueblo Campus
Denver Public Schools
Greeley/Evans School District
Poudre School District
University of Colorado Health - North (Formerly -Poudre Valley Health System - PVHS)
Rocky Mountain National Park
Thompson School District
University of Colorado - Boulder
University of Colorado - Colorado Springs
University of Colorado - Denver
University of Colorado Health Sciences Center
University of Northern Colorado
Other (In the box below, list your study location if not checked above. You may also list details of your already-checked location (e.g., specific school within a school district).

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* * * General Checklist * * *

General Checklist

Select All That Apply :

X Proposed Start Date (cannot be before IRB approval): Sept. 25, 2016

Sponsored Project (Check if you will be funded OR if you have or plan to submit a grant application in association with this protocol)
NSF Sponsored (Please upload mandatory Data Management Plan in the Attachment section)
FDA or EPA-regulated research. Please contact the CSU Quality Assurance Manager, Cat Bens, at 970-491-5445 to determine if your study is under Good Laboratory, Good Clinical, or Good Manufacturing Practices (GLP, GCP, GMP).
Training Grant
Clinical Trial. To register your trial on Clinicaltrials.gov, please contact Cat Bens, CSU Quality Assurance

Manager and Clinical Trails Administrator at: 970-491-5445.

Project is associated with the Colorado School of Public Health - CSPH(faculty and/or student)

Cooperating/Collaborating Institution(s) Institution where recruitment will occur OR Institution where Collaborating PI will conduct associated research.

Interview

Questionnaire/Survey

Subjects will be compensated for participation

Thesis or Dissertation Project

ÃÂ Radioisotopes/radiation-producing machines, even if standard of care. Please contact Jim Abraham, Radiation Safety Officer for questions related to use of all radiation-producing machine: 970-491-3736; james.abraham@colostate.edu. Upload your radiation-use approval (if available) or your Radiation Safety Training certificate in the attachment section.

Human blood, cells, tissues, or body fluids. You will need to obtain IBC approval if you check this box. For information regarding IBC approval, contact Christine Johnson, IBC Coordinator: christine.johnson@colostate.edu

Tissues to be stored for future research projects

Tissues to be sent out of this institution as part of a research agreement

Human Embryos. You will need to obtain IBC approval if you check this box. For information regarding IBC approval, contact Christine Johnson, IBC Coordinator: christine.johnson@colostate.edu

Human Embryonic Cells? Provide NIH Code Number(s) or state that no federal funding will be used to support this research. You may need to obtain IBC approval if you check this box. For information regarding IBC approval, contact Christine Johnson, IBC Coordinator: christine.johnson@colostate.edu

Use of Patient-related equipment? If Yes, specify what equipment is being used.

Medical equipment used for human patients/subjects also used on animals. For questions regarding animal use approval, contact Elaine Kim, IACUC Senior Coordinator: 491-0236

Protocol involves studying potentially addicting drugs. For questions regarding approval for possession of controlled substances, contact Chris Giglio, DRC Coordinator: 491-4830; Chris.Giglio@colostate.edu.

Investigational drugs, reagents, or chemicals (IND)

Commercially available drugs, reagents, or other chemicals administered to subjects (even if they are not being studied)

X Investigational Device (IDE)

Cancer Subjects (e.g., clinical trials, behavior/prevention) or Cancer Tissues (e.g., blood, cells, body fluids). You may need to obtain IBC approval if you check this box. For information regarding IBC approval, contact Christine Johnson, IBC Coordinator: christine.johnson@colostate.edu

Other (clarify in text box to the right)

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* * * Funding * * *

Please complete this section if: 1. This protocol will be funded, 2. You have submitted or will submit a grant application associated with this protocol. Please be sure to input your PASS/SP1 number to assist Sponsored Programs in setting up an account for your funds.

If this protocol is funded by the NIH or NSF, or will lead to the regulatory involvement of the FDA or EPA, please be certain you are cognizant of any specific regulatory requirements for data acquisition, storage, retention and sharing, as well as research expenditure allowability, with regard to this IRB protocol.

Funding Checklist

NONE

NOTE: Applicable Federal Grant Application, including competing renewals, must be attached in the Attachment Section (#16). Applicable investigator's brochure and sponsor's protocol must also be attached in section #16 for all industry-sponsored clinical trials.

Funding - Grants/Contracts

Funding - Fellowships

Funding - Other

Gift Funding

Dept. Funding

Other Funding

Other Fund Name	Rocky Mountain ACSM
Account #, if known	n/a

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* * * Expedited Paragraphs * * *

PLEASE READ: This online application is for projects that will be reviewed by the IRB via the expedite or full-board review process. The criteria for expedited review are listed below. Review and check what expedite criteria is/are appropriate for your project. NOTE: If your research involves or may involve greater than minimal risk, an element of deception, or is FDA-regulated research, do NOT check any of the expedited criteria listed below. Your protocol will then be reviewed by the full-board at their next regularly scheduled meeting. If your project meets the exempt criteria, please submit your exempt application via email to: RICRO_IRB@mail.colostate.edu. Information regarding exempt applications can be found here: http://ricro.colostate.edu/IRB/ExemptReview.html

Expedite Criteria:

1. Clinical studies of drugs and medical devices only when condition (a) or (b) is met.

   a) Research on drugs for which an investigational new drug application (21 CFR Part 31,32) is not required. (Note: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.)

   b) Research on medical devices for which

      i) An investigational device exemption application (21 CFR Part 812) is not required; or
      ii) The medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.

2. Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:

   a) From healthy, nonpregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8- week period and collection may not occur more frequently than 2 times per week; or

   b) From other adults and children, considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8-week period and collection may not occur more frequently than 2 times per week.

3. Prospective collection of biological specimens for research purposes by non-invasive means.

4. Collection of data through non-invasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.)

Examples:

   a) Physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject's privacy;

   b) Weighing or testing sensory acuity;

   c) Magnetic resonance imaging;

   d) Electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow, and echocardiography;

   e) Moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

5. Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for nonresearch purposes (such as medical treatment or diagnosis). (NOTE: Some research in this paragraph may be exempt from the HHS regulations for the protection of human subjects. 45 CFR 46.101(b)(4). This listing refers only to research that is not exempt.)

6. Collection of data from voice, video, digital, or image recordings made for research purposes.

7. Research on individual or group characteristics or behavior(including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies. (NOTE: Some research in this category may be exempt from the HHS regulations for the protection of human subjects. 45 CFR 46.101(b)(2) and (b)(3). This listing refers only to research that is not exempt.)

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* * * Purpose,Study Procedures,Background * * *

Original Protocol Number (e.g., 07-226H)

Title (Please indicate if the protocol title is different from the proposal title)

Can transcranial direct current stimulation improve ambulation and fatigue resistance in people with MS?

Complete Sections 1 - 16. Specify N/A as appropriate. Do not leave any required sections blank.

1. Purpose of the study

a) **Provide a brief lay summary of the project in <200 words. The lay summary should be readily understandable to the general public, and is, for example, what would be released to a newspaper if requested.**

In this project we will be using non-invasive brain stimulation on people with multiple sclerosis (PwMS) to improve leg muscle function. Two groups of participants will be recruited. One group will perform strength testing with and without the brain stimulation. After completing the strength testing they will walk for six minutes to see if any increases in strength translate into improve mobility. The second group will perform a fatigue task, pulling against a wire at a low level of force, with and without the brain stimulation. This type of brain stimulation has been shown to transiently improve strength and fatigue measures in other populations, e.g. aged, Parkinson's, and improve cognitive abilities in people with multiple sclerosis. It is our hope that the increases in performance seen in other patient groups will also occur in people with multiple sclerosis. Future investigations will look to apply the non-invasive brain stimulation technique during physical rehabilitation to improve short and long term outcomes related to physical function.

b) **What does the Investigator(s) hope to learn from the study?**

We expect to show that transcranial Direct Current Stimulation (tDCS) is an effective method for improving neuromuscular function in PwMS. With this information we plan to investigate the concurrent use of tDCS and physical rehabilitation and identify if tDCS can increase the gains seen with traditional PT and if these improvements last longer compared to when only physical therapy is performed.

c) **Proposed Start Date (may not precede IRB approval date):**

Oct. 1, 2016

2.

Study Procedures (If this is a student project, the methods section of the thesis or dissertation proposal must be attached in section #16 - Attachment section.)

a) **In lay language, describe all the procedures, from screening through end-of-study, that the human subject must undergo in the research project, including study visits, drug treatments, randomization and the procedures that are part of standard of care. Please note: Do NOT respond "See Attachment Section." If you would like to add tables, charts, etc., attach those files in the Attachment section (#16).**

To investigate the effects of tDCS on strength and fatigue of the leg muscles in patients with multiple sclerosis (MS) we will employ and randomized blinded cross-over design. Once accepted into the study participants will be randomized into 1 of 4 groups. Group 1 and 2 will perform leg strength testing followed by a 6 minute walk test. Groups 3 and 4 will perform a fatigue task. Each group will perform the same procedures during 2 different visits with 1 visit having a tDCS sham procedure performed and 1 visit performing the task with tDCS. The order of the sham / treatment will be based on the participant's group assignment. Each visit will be separated by at least 7 days. See attachment for proposal timeline.

Participant Recruitment:

Prospective participants will be recruited from the: Integrative Neurophysiology Laboratory's (INPL) participant database; the clinical practice of Dr. William Shaffer, Banner Health, Greeley CO; and through advertisements in the Colorado and Wyoming Chapter of the National MS Society newsletters. All experimental procedures will be performed in the INPL (Director: Thorsten Rudroff, PhD, FACSM). Interested individuals will perform an initial screening via an online questionnaire, hosted by Qualtrics, which has an agreement with the College of Health and Human Sciences. Contact information for the prospective participants' information will be accessible only to the research staff according to HIPPA regulations. After completion of the online screening form, INPL personal will contact 40 eligible participants, 10 for each group, via phone to confirm their participation and schedule the participant's first visit. Once eligibility is confirmed participants will be randomly assigned to 1 of the 4 groups using a random number generator. If by chance a group fills, 10 participants assigned, before the others that number will then be removed to ensure each group has a similar size.

Experimental Sessions:

The experimental protocol for this study consists of two testing sessions. The following procedures are common to the Strength Group and the Fatigue Group in session 1. Upon arrival to the INPL the investigators will explain the protocol and received signed informed consent from the participants. Participants will also complete the Fatigue Severity Scale (FSS) and the Beck's Depression Inventory (BDI) questionnaires. Body composition will be assessed via Dual-Energy X-Ray Absorptiometry (DXA) utilizing standard guidelines set forth by the Department of Health and Exercise Science. Following consent, questionnaires, and DXA each participant will being procedures specific to their randomized group. Group 1 = strength testing, tDCS → Sham; Group 2 = strength testing, Sham → tDCS; Group 3 = fatigue testing, tDCS → Sham; Group 4 = fatigue testing, Sham → tDCS

Strength Group Session 1
After completion of the questionnaires participants will begin strength testing of the knee extensors/flexors, planter/dorsi flexor muscle groups. The participants will perform these measurements while seated with the hip, knee, and ankle at 90 degrees of flexion. All procedures, including those for the fatigue group, will be performed with the participants in this positon. Between muscle group testing and tDCS application participants will be allowed to get up and stretch as needed. A strap attached to a linear force transducer (Noraxon, Scottsdale AZ, USA) will be placed around the participant's ankle or metatarsals. Once in the proper position participants will be verbally encouraged to increase to maximal isometric force output over 3 seconds, continue maximal isometric force output for 1-2 more seconds , and then relax. After each maximal voluntary contraction (MVC) the participants will recover for no less than 60 seconds. Each muscle group will be tested 3-5 times, or until there is no further increase in force produced or if force produced is lower than the previous trial. Both the right and left legs will be tested.

After the initial MVCs are performed participants will be asked to self-report their more- and less-affected legs. Investigators will confirm the self-reported values with the results from the strength testing. Once the more-affected leg has been determined surface electromyography (sEMG) electrodes will be placed on the rectus femoris, vastus lateralis, and vastus medialis oblique, -longus. Prior to performing the experimental paradigm, we will use Transcranial magnetic stimulation (TMS) (Magstim Rapid magnetic stimulator (The Magstim Company Ltd, Spring Gardens, Whitland, Carmarthenshire, UK)) and a focal figure of eight coil (diameter of each wing 70 mm) to identify the right hemisphere M1 hotspot for the left leg extensors. The coil will be placed tangential to the scalp with the handle pointing 90° away from the midline (Groppa et al., 2010). The optimum site in the right M1 (hotspot) for eliciting motor responses in the left leg extensors will be identified at supra-threshold intensity. Resting motor threshold (RMT) will be determined to the nearest 1% of the maximum stimulator output. Using standard protocol, the RMT will be defined as the minimum stimulus intensity that elicited MEPs of 50 mV in at least 5 out of 10 consecutive trials (Triggs et al. 1994).

Once the leg motor cortex of the more-affected side (left or right) has been identified via TMS, a tDCS device (Neuroelectrics Inc., Simi Valley, CA, USA) will deliver a small direct current through two sponge surface electrodes (3cm × 3cm, soaked with 15 mM NaCL)(Dundas et al. 2007). The anodal electrode will be placed over the representation of the motor cortex for the more affected leg, and a second electrode will be placed on the forehead above the contralateral orbit. The intensity of the tDCS will be 2 mA applied for 10 minutes, starting at 0 and increasing to 2 mA over a 30 second period of time. At the 9:30 time point the current will gradually be reduced from 2 mA to 0 mA. Anodal tDCS with these parameters has been reported to change the excitability of the leg motor cortex without inducing side effects (Jeffery et al. 2007). The used parameters are in accordance with a safety criterion and far below the threshold for tissue damage (Nitsche et al. 2003). The voltage during tDCS application will be less than 10 V. During the application of the tDCS current participants will perform strength testing for more-affected side using the same procedures as the initial MVC acquisition. All MVC will be collected within the 10 min tDCS stimulation time. Participants receiving a sham condition will only receive the initial 30 seconds of stimulation, after which the current will be set to 0. These parameters for sham stimulation were chosen based on previous reports that the perceived sensations on the skin, such as tingling, usually fade out in the first 30 s of tDCS (Nitsche et al. 2003; Paulus, 2003). The participants and the investigator performing the MVC testing will be blinded to the tDCS condition. Participants will not be told their strength values until the end of all testing sessions.

After completion of the tDCS/Sham strength assessment participants will perform a 6 minute walk test. The test will be performed in a cordoned off hallway with 2 cones placed 30 meters apart. Once the participants begin walking, a timer will be started and the distance covered every min will be recorded. Participants are allowed to stop and rest during the test if required. Every minute during the walk test participants will be asked their rating of perceived exertion (RPE, 0-10 scale) (Dalgas et al. 2014)

Strength Group Session 2
After no less than 7 days, participants will return to the INPL to perform their final session. All procedures for Session 2 will be the same as in Session 1, except that participants who received tDCS will now receive sham stimulation and those that received the sham treatment will receive tDCS.

In all sessions both, participants and raters will be blinded to the intervention type. The experimenter who

will apply the intervention (real tDCS or Sham) will be different from the experimenter determining the outcome measures.

Fatigue Group Session 1
Once consent, questionnaires, and DXA have been completed, MVCs of the right and left knee extensors will be performed using the same methods stated before. After MVC performance participants will be asked which is their more-affected leg and this answer will be compared to the results of the MVC testing. Once the more-affected leg is determined the investigators will use the same TMS procedures as above to identify the more-affected leg's representation in the motor cortex. The anode tDCS electrode will then be place in this spot, and stimulation will begin 5 min prior to the start of the fatigue task. After 30 secs the current will be lowered to 0 for the Sham group. The treatment group will receive stimulation until the end of the fatigue task or for an additional 15 min, whichever condition occurs first. tDCS blinding and procedures are the same as they are for the strength group. Both participant and investigator will be blinded to the treatment.

The fatigue task will consist of the participants performing an isometric contraction of the knee extensors. Participants will be positioned with the hip, knee, and ankle of the more-affected leg at 90 degrees of flexion. Just prior to the initiation of the fatigue task the participant will perform 1 MVC, and 30% of this force output will be the target output of the fatigue task. Visual feedback will be provided on a computer monitor. Participants will perform the task until they can no longer generate the needed force (within 5% of the target value for 5 seconds), or they say they want to stop. At every 1 minute interval the participant will be asked to provide their rating of perceived exertion (RPE) based on the modified Borg 10 point scale. The required leg position will be monitored by visual inspection, and feedback will be given to the subject by the same investigators for all experiments. Immediately after task failure another MVC with the knee extensors will be performed to quantify the decline in strength.

Fatigue Group Session 2
After no less than 7 days, participants will return to the INPL to perform their final session. All procedures for Session 2 will be the same as in Session 1, except that participants who received tDCS will now receive sham stimulation and those that received the sham treatment will receive tDCS.

In all sessions both, participants and raters will be blinded to the intervention type. The experimenter who will apply the intervention (real tDCS or Sham) will be different from the experimenter determining the outcome measures.

Electromyography (EMG)

During all strength and fatigue testing EMG signals will be recorded with bipolar surface electrodes that will be placed over the vastus medialis oblique, vastus medialis longus, rectus femoris, vastus lateralis, and biceps femoris. The electrodes will be attached according to landmarks between the innervation zone and the end of the tendon (Rainoldi et al. 2004, 2007). The EMG signals will be amplified (x 2,000), band-pass filtered (13–1,000 Hz; Noraxon) and recorded on a computer.

b) Explain why human subjects must be used for this project.

The goal of this project is to determine if tDCS can increase leg muscle strength and fatigue resistance in people with MS. Therefore all clinical testing needs to be performed in the patient population that is being studied.

c) Alternative Procedures. If the proposed study is a clinical trial of a drug, vaccine, device or treatment, describe alternative procedures, if any, that might be advantageous to the subject. Describe the important potential risks and benefits associated with the alternative procedure(s) or course(s) of treatment. Any standard treatment that is being withheld must be disclosed. This information must be included in the consent form.

N/A

d) If the proposed study is a clinical trial of a drug, vaccine, device or treatment, will it be possible to continue the more (most) appropriate therapy for the subject(s) after the conclusion of the study?

N/A

e) Study Endpoint. If the proposed study is a clinical trial of a drug, vaccine, device or treatment, what are the guidelines or end points by which you can evaluate the alternative treatments during the study? If one treatment proves to be clearly more effective than another (or others) will the study be terminated before

treatment proves to be clearly more effective than another (or others) will the study be terminated before the projected total subject population has been enrolled? When will the study end if no important differences are detected?

N/A

f) State if deception will be used. If so, provide a rationale and describe debriefing procedures. Submit a debriefing script in the Attachment Section (#16).

N/A

3. Background

a) Describe past experimental and/or clinical findings leading to the formulation of the study, if applicable.

Our previous studies showed asymmetries in muscle activities during walking in PwMS (Rudroff et al.2015, Ketelhut et al. 2015). The next step is now to investigate the underlying mechanisms and possible rehabilitation treatments.

b) Describe any animal experimentation and findings leading to the formulation of the study, if applicable.

N/A

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* * * Radioisotopes or Radiation Machines * * *

You selected NO for Radioisotopes in the General Checklist. If you would like to add Radioisotopes, change the selection to YES in general Checklist.

4.

Radioisotopes or Radiation Machines Please note: For projects requiring radiation procedures, please contact the CSU Radiation Control Office (RCO). For more information see: http://www.ehs.colostate.edu/WRad/Home.aspx :

a) If applicable, summarize in lay language the radiographic diagnostic and therapeutic procedures associated with this protocol.

The DEXA scan that will be performed during this study uses radiation to assess bone mineral density and body composition at pre treatment.

b)

Are the radiation procedures being performed a normal part of the clinical management for the medical condition that is under study (Standard of Care) or are the procedures being performed because the research subject is participating in this project (extra CT scans, more fluoroscopy time, additional Nuclear Medicine Studies, etc.,) (Not Standard of Care)? If some procedures are Standard of Care and some are Not Standard of Care, check both boxes.

NOT STANDARD OF CARE	STANDARD OF CARE
If it is not standard of care, complete the rest of this section. Provide the CSU RCO approval information	If it is only standard of care, skip the rest of this section.

CSU Radiation Control Office approved protocol number:

CSU Radiation Control Office protocol approval date:

For more information, see the RCO website at:http://www.ehs.colostate.edu/Wrad/home.aspx or Contact: James Abraham, Radiation Safety Officer, at 970-491-3736.

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* * * Medical Equipment for Human Subjects and Laboratory Animals; Investigatiional Devices * * *

5. Medical Equipment for Human Subjects

If medical equipment is being used for human subjects/patients, describe this equipment and indicate if the use is normal practice for the population under study. You may have already described this equipment in the Study Procedures section. If you have already listed this information in the Study Procedures Section, please do not duplicate this information here. In the space below, input N/A if not applicable, indicate if this is already listed in the Study Procedures Section, or describe the equipment.

N/A

6. Investigational Devices

Please list in the space below all Investigational Devices to be used on Subjects.

Investigational Devices

Investigational Devices

Describe the device(s) to be used

ActivaDose II Iontophoresis Delivery Unity

Device Name ActivaDose II Iontophoresis Delivery Unity

Manufacturer ActivaTek, Inc.

Significant risk Y **Non-Significant risk**

IDE #

Rationale for Non-Significant Risk Device

Class 2 device.

If a non-significant risk device study is indicated, provide rationale for the device being non-significant risk. Please state if you need IRB guidance on whether this is a significant or non-significant risk device.

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* * * Drugs, Reagents, or Chemicals * * *

7. Drugs, Reagents, or Chemicals

a) **Please list in the space below all investigational drugs, reagents or chemicals to be administered to subjects during this study.**

b) **Please list in the space below all commercial drugs, reagents or chemicals to be administered to subjects during this study.**

Please read the IND Statements

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* * * Subject Population (a-g) * * *

8.

Subject Population - In the space below, please detail the participants that you are requesting to recruit (include requested participant number and description of each group requested). (Input N/A if not applicable)

a) **Requested Participant Description (Include number of participants that you plan to study and description of each group requested, if applicable).**

N/A

b) **What is the rationale for studying the requested group(s) of participants?**

To investigate the effects of tDCS on leg muscle strength and fatigue. The research team has experience with all the methods involved.

c) **If applicable, state the rationale for involvement of potentially vulnerable subjects to be entered into the study, including minors, pregnant women, economically and educationally disadvantaged, or decisionally impaired subjects. Specify the measures being taken to minimize the risks and the chance of harm to the potentially vulnerable subjects.**

N/A

d) **If women, minorities, or minors are not included, a clear compelling rationale must be provided. Examples for not including minors: disease does not occur in children; drug or device would interfere with normal growth and development; etc.**

N/A

e) **State if any of the subjects are students, employees, or laboratory personnel. They should be presented with the same written informed consent. If compensation is allowed, they should also receive it.**

N/A

f) **Describe how potential subjects will be identified for recruitment (e.g., chart review, referral from individual's treating physician, those individuals answering an ad). How will potential participants learn about the research and how will they be recruited (e.g., flyer, email, web posting, telephone, etc.)? Attach recruitment materials in the Attachment Section (#16). Important to remember: potential subjects may not be contacted before IRB approval.**

Prospective participants will be recruited from the Integrative Neurophysiology Laboratory's (INPL) participant database, the clinical practice of Dr. William Shaffer, Banner Health, Greeley CO, and through advertisements in the Colorado and Wyoming Chapter of the National MS Society newsletters. All experimental procedures will be performed in the INPL (Director: Thorsten Rudroff, PhD, FACSM). Interested individuals will perform an initial screening via an online questionnaire, hosted by Qualtrics, which has a contract with the College of Health and Human Sciences. Contact information for the prospective participants' information will be accessible only to the research staff according to HIPPA regulations. After completion of the online screening form, INPL personal will contact eligible participants via phone. INPL staff will schedule the participants' first visit (30 total).

g) **If applicable, provide rationale for the inclusion of healthy volunteers in this study. Specify any risks to which these healthy volunteers may possibly be exposed. Specify the measures being taken to minimize the risks and the chance of harm to these volunteers.**

N/A

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* * * Subject Population (h-m) * * *

8. Subject Population (Input N/A if not applicable)

h) Inclusion and Exclusion Criteria (e.g., Participants must have 20/20 vision, Participants must be 30-45 years of age, etc.)

Identify inclusion criteria.

Medically diagnosed with MS, 30-60 years of age, Moderate disability (Patient Determined Disease Steps score 2-6), self-reported differences in function between the legs (2-5 on a 1-5 scale).

Identify exclusion criteria.

•A relapse of disease symptoms in the last 60 days
•A condition unrelated to MS that would exacerbate fatigue, such as anemia, hypothyroidism, shiftwork-related fatigue, B12 deficiency, major sleep disorder, or major depressive disorder
•Medical diagnosis or condition that makes participating in exercise training dangerous, such as major renal, pulmonary, hepatic, cardiac, gastrointestinal, HIV, cancer (other than treated basal cell cancer), other neurological disorders, or pregnancy
•History of heart attack or current diagnosis of cardiovascular disease
•History of seizure disorders (or on medications known to lower seizure threshold),
• Hydrocephalus (i.e. buildup of fluid in the brain)
•Alcohol dependence or abuse (>2 drinks/day), or present history (last six months) of drug abuse
•History of significant traumatic brain injury
•Pregnancy
•Recent hospitalization (within the last 3 months) or enforced bed rest/sedentary state.
•Presence of metal is present or implanted device or metal object that is not safe for TMS.
•Presence of holes or fissures of the cranial bones

i) Describe your screening procedures. Attach your screening document(s) (e.g., health history questionnaire) in the Attachment Section (#16).

Prospective participants will be screened via an online questionnaire. This questionnaire will gather contact information, date of birth, height, weight, self-reported disability status, and cardiovascular risk factors.

j) Describe how you will be cognizant of other protocols in which subjects might be participating. Please explain if subjects will be participating in more than one study.

This will be the only study participants will be in.

k) Compensation. Explain the amount and schedule of compensation, if any, that will be paid for participation in the study. Compensation includes food, gift cards, money, tokens, etc. Include provisions for prorating payment, if applicable. Compensation should be prorated if several activities are involved for different time periods (e.g., $10 for session #1, and $10 for session #2).

Subjects in the fatigue group will be compensated $20 upon completion of the study.

l) Costs. Please explain any costs that will be charged to the subject.

None, participants are only responsible for their transportation to/from campus.

m) Estimate the probable duration of the entire study. This estimate should include the total time each subject is to be involved and the duration the data about the subject is to be collected (e.g., This is a 2-year study. Participants will be interviewed 3 times per year; each interview will last approximately 2 hours. Total approximate time commitment for participants is 12 hours). These times should be consistent with the time commitment listed on the consent document.

Participants will be expected to spend approximately 2.5-3 hours split over 2 session. We expect data collection to last 6 months.

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* * * Risks * * *

9. Risks (Input N/A if not applicable)

US Department of Health & Human Services (HHS) Regulations define a subject at risk as follows: "...any individual who may be exposed to the possibility of injury, including physical, psychological, or social injury, as a consequence of participation as a subject in any research, development, or related activity which departs from the application of those accepted methods necessary to meet his needs, or which increases the ordinary risks of daily life, including the recognized risks inherent in a chosen occupation or field of service."

a) PI's evaluation of the overall level of Risk. (Please check one: minimal or > minimal.)

Y **Minimal (everyday living)**

> Minimal (greater than everyday living)

b)

For the following categories include a scientific estimate of the frequency, severity, and reversibility of potential risks. Wherever possible, include statistical incidence of complications and the mortality rate of proposed procedures. Where there has been insufficient time to accumulate significant data ON risk, a statement to this effect should be included. (In describing these risks in the consent form to the subject, it is helpful to use comparisons which are meaningful to persons unfamiliar with medical terminology.) Address any risks related to:

1. **Use of investigational devices. Please include the clinical adverse events (AEs) associated with each of the devices with an indication of frequency, severity and reversibility. This information can often be found in the Investigator(s) brochure.**

N/A

2 **Use of investigational drugs. Please include the clinical AEs associated with each of the drugs with an indication of frequency, severity and reversibility. This information can often be found in the Investigator(s) brochure.**

N/A

3 **Use of commercially available drugs, reagents or chemicals. Please include the clinical AEs associated with each of the drugs with an indication of frequency, severity and reversibility. This information can often be found in the package insert provided by the manufacturer.**

N/A

4 **When performing procedures, please include all investigational, non-investigational and non-invasive procedures (e.g., surgery, blood draws, treadmill tests).**

Participants will perform maximal voluntary strength tests with the leg extensors, -flexors, and dorsiflexors and a 6 min walk test to determine how far they can walk in 6 min. They will also perform a fatigue task (isometric contraction) with the more affected leg.
There is a risk of muscle/tendon strain with the exercises.

5 **Radioisotopes/radiation-producing machines(e.g., X-rays, CT scans, fluoroscopy).**

N/A

c)

For the following categories, include an estimate of the potential risk, if applicable.

1. Physical well-being.

Potential risks include: skin irritation to surface electromyography electrodes, muscle cramps/spasms during strength testing.

tDCS safety
tDCS is a non-invasive brain stimulation technique in which a very weak electrical current is applied to the scalp. tDCS has been conducted on humans and animals for many years and no evidence has emerged to suggest that it is harmful or has ever induced a serious side effect. However, the safety of tDCS is dependent on current strength, electrode size, and stimulation duration. Accordingly, these parameters have been investigated to establish safe and effective stimulation parameters for tDCS applications in research involving human subjects. The only side effects that have been reported when proper guidelines are followed are temporary tingling, itching, headache, or skin redness under the electrodes in some subjects. For example, a 2008 review of the approximately 100 human tDCS studies up until that time on healthy adults and patients found that 64 of these studies reported no side effects, 24 studies reported a temporary itching or tingling under the electrodes in some subjects, and one study reported skin redness. Furthermore, these slight side effects were of equal occurrence in subjects that received placebo stimulation in 7 studies. In addition, only two subjects in these 100 studies reported a mild headache. Similar findings have recently been reported in research and review articles (Nitsche et al. 2008; Hummel et al. 2008).

Physiological studies have also assessed the safety of tDCS when applied within the aforementioned stimulation guidelines. For example, there was no neuronal damage as measured by serum neuron-specific enolase (Stagg & Nitsche, 2011) or MRI measures of edema using contrast enhanced and diffusion-weighted MRI measures following administration of tDCS (Nitsche et al. 2004). Furthermore, tDCS did not negatively alter measures of neuropsychological function and EEG activity (Iver et al. 2005). Accordingly, rat studies using tDCS models emulating tDCS applied to humans (Liebetanz et al. 2009) showed that the current density needed to induce tissue damage or lesions was about 1429 mA/cm2, whereas the current densities used in human studies are between 0.04 and 0.08 mA/cm2 and in this proposal are 0.029 mA/cm2. In conclusion, the tDCS stimulation parameters in this study are identical to the most common in the literature and have been proven to be exceptionally safe and well-tolerated.

The probablilty is very unlikely that harm may occur (see above). Based on the availiable literature a slight headache should be the worst possible negative effect and should be very rare. In this case, non-prescription medication should relieve the headache within 1-2 hours.

Risks will be minimized by using safe, well-established procedures and strict monitoring of each experimental session. Risks are minimized by using stimulation parameters that are well-described, within international guidelines, and within the range of those used in hundreds if not thousands of studies (see above).

TMS safety
TMS is a non-invasive brain stimulation technique that can be used for both diagnostic and therapeutic procedures. The single and paired-pulse TMS techniques performed in this study have been used extensively in thousands of research studies and on tens of thousands of subjects in the United States and around the world. Single and paired pulse TMS techniques are considered very safe (Hallet, 2000, 2007) when accepted guidelines are followed (Wassermann et al. 1998). Finally, no long-term risks have been reported in the aforementioned review articles involving the use of TMS. In general, the risks associated with TMS are very minimal (Anand et al. 2002; Anderson et al. 2006; Loo et al. 2008). There is a very small risk of seizures if rTMS is done with very intense, high frequency stimulation or with trains of stimulation separated by a second or less (Anand et al. 2002; Anderson et al. 2006; Loo et al. 2008). Such intensity, frequency and repetition rate will not be used in this study as the study does NOT include rTMS and only single and paired pulse TMS methods will be employed. For most people, the single and paired pulse stimulation is not painful, but

occasionally slight discomfort or headache can occur. The headaches go away quickly with nonprescription medication. The noise caused by TMS pulses may affect hearing; therefore, subjects will be fitted with earplugs during TMS testing. Finally, there is no medical risk associated with the surface EMG recordings of the muscle responses to TMS.

2. **Psychological well-being.**

None

3. **Economic well-being.**

None

4. **Social well-being.**

None

d) **In case of overseas research, or working with a specific race/ethnicity in the United States, provide background on what experience the Investigator(s) have with the proposed population. Describe qualifications/preparations that enable the Investigator(s) to evaluate cultural appropriateness and estimate/minimize risks to subjects.**

N/A

e) **Special Precautions. Describe the planned procedures for protecting against or minimizing potential risks. If appropriate, include the standards for termination of the participation of the individual subject. Discuss plans for ensuring necessary medical or professional intervention in the event of adverse effects to the subjects.**

All research staff are certified in CPR, AED, and First Aid by the American Red Cross. Participants are freely available to stop any procedure at any time.

f)

Data Safety Monitoring

N **Is there a Data Safety Monitoring Board (DSMB)?**

If yes, describe its role and indicate who set up the Data Safety Monitoring Board (e.g., sponsor or Protocol Director).

Describe the data and safety monitoring plan developed to ensure the safety of participants and the validity and integrity of research data. Monitoring should be commensurate with risks and with the size and complexity of the trials.

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* * * Benefits, Procedures to Maintain Confidentiality * * *

10. Benefits (Input N/A if not applicable)

a) **Describe the potential benefit(s) to be gained by the subjects. If there is no direct benefit to the subjects describe how the results of the study may benefit society or a particular group.**

There is no personal benefit associated with this protocol, although the outcomes may help improve rehabilitative procedures for people with MS who have fatigue and leg strength asymmetries.

11. Procedures to Maintain Confidentiality

a) **Describe the procedures that protect the privacy of the subjects and maintain the confidentiality of the data. If a linked list is used, explain when the linked list will be destroyed. Provide a sample of the code that will be used, if applicable.**

All data collected, including personal identifiable information will be stored either electronically on Colorado State University secured networks with access restricted to the current investigators. Hard copy data will be stored in a locked file cabinet that only research personnel have access too. At night second story of the Health and Exercise Science Department is restricted to authorized key holders, and the room in which the file cabinet is located is restricted to only current laboratory staff.

b) **If information derived from the study will be provided to the subject's personal physician, a government agency, or any other person or group (other than the research team), describe to whom the information will be given and the nature of the information, if applicable.**

N/A

c) **Specify where and under what conditions study data will be kept, how samples will be labeled, who has access to the data, and what will be available and to whom. Federal regulations require that study data and consent documents be kept for a minimum of three (3) years after the completion of the study by the PI. For longitudinal projects and federally regulated studies, the PI may be required to keep the data and documents for a longer time period.**

All data collected, including personal identifiable information will be stored either electronically on Colorado State University secured networks with access restricted to the current investigators. Hard copy data will be stored in a locked file cabinet that only research personnel have access too. At night second story of the Health and Exercise Science Department is restricted to authorized key holders, and the room in which the file cabinet is located is restricted to only current laboratory staff

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*** * * Potential Conflict of Interest * * ***

12. Potential Conflict of Interest

Although you have already submitted CSU's official Conflict of Interest form (FCOI/COI/COC) to the University, it is the IRB's responsibility to ensure that conflicting interests related to submitted protocols do not adversely affect the protection of participants or the credibility of the human research protection program at CSU. Please answer questions a-d below. Please note that if you indicate that you have a potential financial or professional conflict of interest in relation to this protocol, your CSU FCOI/COI/COC Reporting Form must reflect this potential conflict. Link to CSU's Conflict of Interest policy: :http://www.facultycouncil.colostate.edu/files/manual/sectiond.htm#D.7.7

a)	N	**In connection with this protocol, do you or any of the protocol investigators or their immediate family members (i.e., spouse and legal dependents, as determined by the IRS) have a potential financial or professional conflict of interest?**
b)	N/A	**If you do have a potential conflict of interest, is this reported in your current FCOI/COI/COC?**
c)	N/A	**If you do have a potential conflict of interest, is there a management plan in place to manage this potential conflict?**
d)	N/A	**If you do have a potential conflict of interest, is this potential conflict of interest included in your consent document (as required in the Management Plan)?**

If you have reported a possible conflict of interest, the IRB will forward the title of this protocol to your Research Associate Dean to complete your COI file.

For more information on CSU's policy on Conflict of Interest, please see the Colorado State University Academic Faculty and Administrative Professional Manual Sections D.7.6 & D.7.7. :http://www.facultycouncil.colostate.edu/files/manual/sectiond.htm#D.7.7

Link to CSU's Conflict of Interest Policy: http://www.provost.colostate.edu/index.asp?url=faculty_affairs.

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* * * Informed Consent * * *

13. Informed Consent

NOTE: In order to complete this protocol, you must upload either a Consent Form or an Alteration of Consent Form (i.e., Cover Letter or Verbal Script) OR (if neither of those apply to your project) you must complete the Waiver of Consent information.

In the space below, please provide consent process background information for each Consent Form(s), Alteration of Consent Form(s), or Waiver(s).

Informed Consent

Title	Fatigue Consent 24July2017	
Consent Information Type	Consent	
Sponsor's Consent Version Number: (if any)		
Consent Form Template	X Attachment	Amendment_Consent_tDCS_Fatigue_24July2017 (1) (1)

<a href='http://ricro.colostate.edu/IRB/ConsentAssentTemplates.html' target=_blank Consent Form Samples

Who is obtaining consent? The person obtaining consent must be knowledgeable about the study and authorized by the PI to consent human subjects.

How is consent being obtained?

What steps are you taking to determine that potential subjects are competent to participate in the decision-making process?

Title	Strength Consent 06JUNE2017	
Consent Information Type	Consent	
Sponsor's Consent Version Number: (if any)		
Consent Form Template	X Attachment	Consent_tDCS_Strength_20170606 (4)

<a href='http://ricro.colostate.edu/IRB/ConsentAssentTemplates.html' target=_blank Consent Form Samples

Who is obtaining consent? The person obtaining consent must be knowledgeable about the study and authorized by the PI to consent human subjects.

How is consent being obtained?

What steps are you taking to determine that potential subjects are competent to participate in the decision-making process?

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14. Assent Background (Complete if applicable)

All minors must provide an affirmative consent to participate by signing a simplified assent form, unless the Investigator(s) provides evidence to the IRB that the minor subjects are not capable of assenting because of age, maturity, psychological state, or other factors.

See sample consent/assent forms at http://ricro.colostate.edu/IRB/ConsentAssentTemplates.html

Provide assent process background information, in the space below, for each Assent Form, Alteration Form (i.e., Cover Letter or Verbal Script), and Waiver.

Assent Background

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* * * HIPAA * * *

15. HIPAA

Are you using PHI*? (See definition below)

Y

Colorado State University is a hybrid entity and does not have a research-related HIPAA policy. If you will be working with a HIPAA covered entity (e.g., Poudre Valley Health System), you will need to follow their HIPAA guidelines. If your project will involve a HIPAA-regulated entity, in the Attachment section (#16) please attach that entity's required HIPAA consent and/or each waiver of authorization or alteration of authorization requested (e.g., waiver of authorization for access to medical records). Include HIPAA authorization language in the consent document(s) as appropriate (e.g., when enrolling subjects).

*Protected Health Information (PHI) is health information with one or more of the following identifiers. For more information see: http://www.hhs.gov/ocr/hipaa/

1. Names
2. Social Security numbers
3. Telephone numbers
4. All geographic subdivisions smaller than a State, including street address, city, county, precinct, zip code, and their equivalent geocodes, except for the initial three digits of a zip code, if, according to the current publicly available data from the Bureau of the Census: (1) The geographic unit formed by combining all zip codes with the same three initial digits contains more than 20,000 people; and (2) The initial three digits of a zip code for all such geographic units containing 20,000 or fewer people is changed to 000
5. All elements of dates (except year) for dates directly related to an individual, including birth date, admission date, discharge date, date of death; and all ages over 89 and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older
6. Fax numbers
7. Electronic mail addresses
8. Medical record numbers
9. Health plan beneficiary numbers
10. Account numbers
11. Certificate/license numbers
12. Vehicle identifiers and serial numbers, including license plate numbers
13. Device identifiers and serial numbers
14. Web Universal Resource Locations (URLs)
15. Internet Protocol (IP) address numbers
16. Biometric identifiers, including finger and voice prints
17. Full face photographic images and any comparable images; and
18. Any other unique identifying number, character, or code (note this does not mean the unique code assigned by the Investigator(s) to code the research data)

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* * * Attachments * * *

16. Attachments

Attach relevant documents here. These could include: Collaborating Investigator's IRB approval and approved documents; Conflict of Interest information; Debriefing Script; Grant/Sub-contract; HIPAA Authorization Form from HIPAA-covered entity; Interview/Focus Group Questions; Investigator's Brochure; Letters of Agreement/Cooperation from organizations who will help with recruitment; Methodology section of associated Thesis or Dissertation project; Questionnaires; Radiation Control Office approval material; Recruitment Material (e.g., flyers, email text, verbal scripts); Sponsor's Protocol; Surveys; Other files associated with the protocol (you can upload most standard file formats: xls, pdf, jpg, tif, etc.) Please be sure to attach all documents associated with your protocol. Failure to attach the files associated with the

protocol may result in this protocol being returned to you for completion prior to being reviewed. Students: Be sure to attach the Methods section of your thesis or dissertation proposal. If this protocol is associated with a grant proposal, please remember to attach your grant.

To update or revise any attachments, please delete the existing attachment and upload the revised document to replace it.

Document Type	**Questionnaire/Survey**
Attachment	Beck_Depression_Inventory
Document Name	Beck_Depression_Inventory

Document Type	**Questionnaire/Survey**
Attachment	FSS
Document Name	FSS

Document Type	**Other Protocol Material**
Attachment	Timeline_tDCS
Document Name	Timeline_tDCS

Document Type	**Other Protocol Material**
Attachment	References
Document Name	References

Document Type	**Other Protocol Material**
Attachment	Device Accountability Log
Document Name	Device Accountability Log

Document Type	**SOP**
Attachment	RestingMotorThreshold_Hotspot_SOP
Document Name	RestingMotorThreshold_Hotspot_SOP

Document Type	**Other Protocol Material**
Attachment	Rossi2009_TMS_Safety
Document Name	Rossi2009_TMS_Safety

Document Type	**Other Protocol Material**
Attachment	HIPAA Release generic
Document Name	HIPAA Release generic

Document Type	**Letters of Agreement.Cooperation**
Attachment	Shaffer Letter _tDCS
Document Name	Shaffer Letter _tDCS

Document Type	**Recruitment Material (e.g., flyers, email text, verbal scripts)**

Attachment	Recruitment_Flyer_tDCS
Document Name	Recruitment_Flyer_tDCS
Document Type	**Questionnaire/Survey**
Attachment	MS_tDCS_pilot_screening_20170606
Document Name	MS_tDCS_pilot_screening_20170606
Document Type	**SOP**
Attachment	ActivaDoseII_manual
Document Name	ActivaDoseII_manual

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* * * Obligations * * *

Obligations (Researcher's Responsibilities)

The Principal Investigator is ultimately responsible for the conduct of the project. Obligations of the Principal Investigator are:

Conduct the research involving human subjects as presented in the protocol, including modifications, as approved by the Department and Institutional Review Board. Changes in any aspect of the study (for example project design, procedures, consent forms, advertising materials, additional key personnel or subject populations) will be submitted to the IRB for approval before instituting the changes (PI will submit the "Amendment/Revision" form);

Provide all subjects a copy of the signed consent form, if applicable. Investigators will be required to retain signed consent documents for three (3) years after close of the study;

Maintain an approved status for Human Subjects Protection training. Training must be updated every three (3) years (Contact RICRO to check your current approval/renewal dates). For more information: Human Subjects Training Completed?

Submit either the "Protocol Deviation Form" or the "Report Form" to report protocol Deviations/Violations, Unanticipated Problems (UPs) and/or Adverse Events (AEs) that occur in the course of the protocol. Any of these events must be reported to the IRB as soon as possible, but not later than five (5) working days. Note that if an event resulted in life threatening injury or death OR an event resulted in substantive harm to the safety, rights or welfare to human subjects, this must be reported to the IRB within 24 hours;

Submit the "Continuing Review" Form in order to maintain active status of the approved protocol. This form must be submitted annually at least four (4) weeks prior to expiration, five (5) weeks for protocols that require full review. If the protocol is not renewed before expiration, all activities must cease until the protocol has been re-reviewed;

Notify the IRB that the study is complete by submitting the "Final Report" form.

X The Principal Investigator has read and agrees to abide by the above obligations.

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* * * Event History * * *

Event History

Date	Status	View Attachments	Letters
08/22/2016	NEW FORM CREATED		
09/01/2016	NEW FORM SUBMITTED	Y	
09/06/2016	NEW FORM PANEL ASSIGNED		
09/09/2016	NEW FORM REVIEWER(S) ASSIGNED		
09/12/2016	NEW FORM REVIEWER(S) ASSIGNED		
10/03/2016	NEW FORM REVIEWER(S) ASSIGNED		
10/25/2016	NEW FORM MOVED		
10/25/2016	NEW FORM APPROVED	Y	Y
11/09/2016	AMENDMENT 1 FORM CREATED		
11/09/2016	AMENDMENT 1 FORM SUBMITTED	Y	
11/11/2016	AMENDMENT 1 FORM APPROVED	Y	Y
06/06/2017	AMENDMENT 2 FORM CREATED		
06/06/2017	AMENDMENT 2 FORM SUBMITTED	Y	
06/07/2017	AMENDMENT 2 FORM REVIEWER(S) ASSIGNED		
07/05/2017	AMENDMENT 2 FORM MOVED		
07/05/2017	AMENDMENT 2 FORM APPROVED	Y	Y
07/26/2017	AMENDMENT 3 FORM CREATED		
07/26/2017	AMENDMENT 3 FORM SUBMITTED	Y	
07/27/2017	AMENDMENT 3 FORM APPROVED	Y	Y
08/02/2017	CONTINUING REVIEW 1 FORM CREATED		
08/24/2017	CONTINUING REVIEW 1 FORM SUBMITTED	Y	
09/08/2017	CONTINUING REVIEW 1 FORM REVIEWER(S) ASSIGNED		
09/20/2017	CONTINUING REVIEW 1 FORM APPROVED	Y	Y
07/12/2018	FINAL FORM CREATED		
07/12/2018	FINAL FORM SUBMITTED	Y	

Consent to Participate in a Research Study
Colorado State University

TITLE OF STUDY: Can transcranial direct current stimulation (tDCS) improve ambulation and fatigue resistance in people with MS?

PRINCIPAL INVESTIGATORS:
The principal investigator is a researcher in the Department of Health and Exercise Science at Colorado State University:

Thorsten Rudroff, Ph.D., FACSM
HES-INPL@mail.ColoState.edu
970-491-8655

WHY AM I BEING INVITED TO TAKE PART IN THIS RESEARCH?
You are an adult aged between 30 and 60 years of age, and you were diagnosed with Multiple Sclerosis.

WHO IS DOING THE STUDY?
Dr. Rudroff and his graduate students John Kindred, Nathan Ketelhut, and Felix Proessl are performing the study in the Integrative Neurophysiology Laboratory.

WHAT IS THE PURPOSE OF THIS STUDY?
The purpose of this study is to determine if a single session of tDCS can increase fatigue resistance of the more affected leg in people with MS.

WHERE IS THE STUDY GOING TO TAKE PLACE AND HOW LONG WILL IT LAST?
The study will take place in the Integrative Neurophysiology Laboratory in the Department of Health and Exercise Science, on the Colorado State University campus. The study will run for approximately 12 months. You will take part in the study for approximately a total of 3 hours over the space of two weeks.

WHAT WILL I BE ASKED TO DO?
You will be asked to participate in two sessions on two different days separated by no less than 7 days. Each visit will last approximately 90min.

If you participate in this study you will perform strength tests of your leg muscles in association with 1 of 2 intervention protocols involving tDCS application (BEFORE and SHAM) with each intervention protocol being performed in a separate session on a different day. Thus, in one session you will receive tDCS before the strength test, whereas in another session you will receive sham tDCS before the strength test.

Upon arrival to the INPL the investigators will explain the protocol procedures and receive signed informed consent from you.

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- Questionnaires: You will fill out to questionnaires relating to fatigue and depression.
- *Body Compostion*: We will perform a Dual-Energy X-Ray Absorptiometry (DXA) scan on you. A very small amount of X-Rays will pass through your body and allow us to measure the amount of muscle, fat, and bone you have.
- *Leg Strength:* The maximal strength of each leg will be measured by having you perform a series of maximal effort knee extension trials. This will be performed one leg at a time up to five times. The activity of your muscles will be measured during this task by placing a series of electrodes on the skin of your legs.
- *Fatigue Task:* The fatigue task will consist of an isometric, no movement of the legs, contraction of the knee extensors. You will be positioned with the hip, knee, and ankle of the more-affected leg at 90 degrees of flexion. The fatigue task will be performed at 30% of your best leg strength test. Visual feedback will be provided on a computer monitor. You will perform the task until you can no longer generate the needed force (within 5% of the target value for 5 seconds), or you say that you want to stop. At every 1 minute interval you will be asked how you feel on a scale from 0 to 10. Your required leg position will be monitored by visual inspection. Immediately after task failure another strength test with the knee extensors will be performed to measure the decline in strength.

tDCS is a non-invasive technique in which a very weak electrical current is applied to the head in order to stimulate the brain. For tDCS, we will place rubber electrodes soaked in salt water or electrode gel over your scalp and forehead. Therefore, one of the electrodes will be placed over your hair, but no additional substances will be put in your hair and no additional preparation of the hair will be conducted. The electrodes will be held in place with a head band. A small current will be passed between the electrodes. You may feel some tingling under the electrodes when the current is first turned on. The stimulation will last for no longer than 20 min.

To find the right location of electrode on your head we will use transcranial magnetic stimulation (TMS). For application of TMS, a wire coil is held on the scalp. A brief electrical current is passed through the coil and creates a magnetic pulse that stimulates the brain. You will hear a click and may feel a pulling sensation on the skin under the coil and there may be a twitch in muscles of the face, arm or leg. During the stimulation, you will be at rest. You will wear a shower cap during the TMS testing and marks will be made on the cap to denote positioning of the coil.

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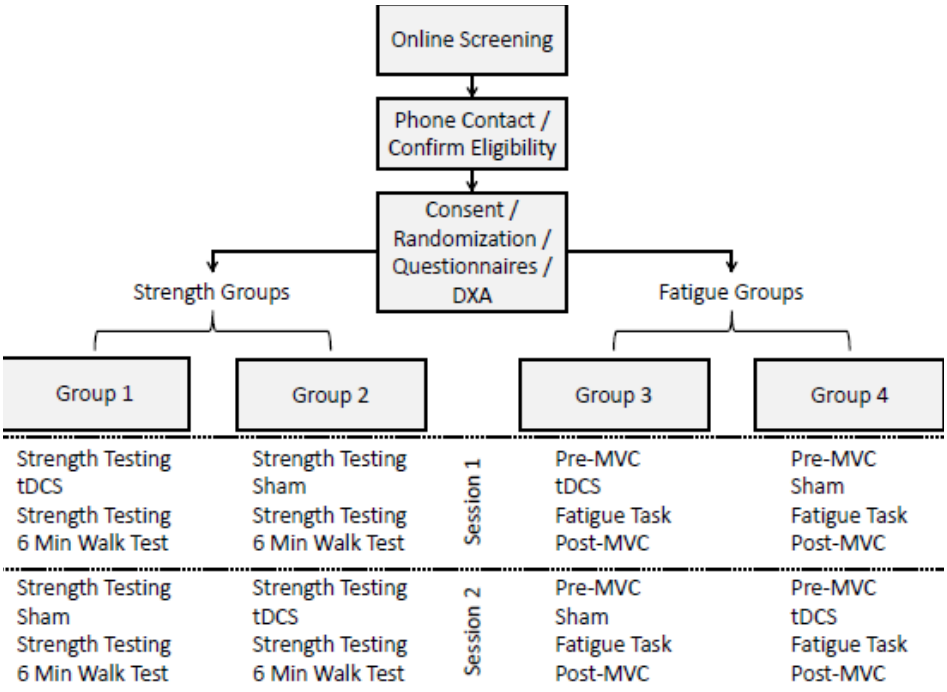

ARE THERE REASONS WHY I SHOULD NOT TAKE PART IN THIS STUDY?

You should not take part in this study if:

- A relapse of disease symptoms in the last 60 days
- A condition unrelated to MS that would exacerbate fatigue, such as anemia, hypothyroidism, shiftwork-related fatigue, B12 deficiency, major sleep disorder, or major depressive disorder
- Medical diagnosis or condition that makes participating in exercise training dangerous, such as major renal, pulmonary, hepatic, cardiac, gastrointestinal, HIV, cancer (other than treated basal cell cancer), other neurological disorders, or pregnancy
- History of heart attack or current diagnosis of cardiovascular disease
- History of seizure disorders (or on medications known to lower seizure threshold), hydrocephalus (buildup of fluid in the brain), or diabetes
- Alcohol dependence or abuse (>2 drinks/day), or present history (last six months) of drug abuse
- History of significant traumatic brain injury or hydrocephalus
- Pregnancy
- Recent hospitalization (within the last 3 months) or enforced bed rest/sedentary state.
- Presence of metal is present or implanted device or metal object that is not safe for TMS.

WHAT ARE THE POSSIBLE RISKS AND DISCOMFORTS?

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It is not possible to identify all potential risks in research procedures, but the researcher(s) have taken reasonable safeguards to minimize any known and potential, but unknown, risks.

Risks of Having a Body composition (DXA) scan

The risks associated with the DEXA are very low. The maximum radiation dose you will receive in this study is less than 1/1000th of the federal and state occupational whole body dose limit allowed to radiation workers (5,000 mrem) (mrem is a unit used to measure radiation dosage). Put another way, the maximum dose from any scan we utilize with this DEXA ranges from 1.2 mrem (Whole body scan) to 12.2 mrem (for several of the regional scans, such as lumbar, femur, and forearm scans). The average annual background radiation you already receive is at least 620 mrem/year. The more radiation you receive over the course of your life, the more the risk increases of developing a fatal cancer or inducing changes in genes. The radiation in this scan is not expected to significantly increase these risks, but the exact increase in such risks is not known. There are no discomforts associated with this procedure.

Risks of tDCS

tDCS has been conducted on humans and animals for many years and no evidence has emerged to suggest that it is harmful or has ever induced a serious side effect. However, the safety of tDCS is dependent on current strength, electrode size, and stimulation duration. Accordingly, these parameters have been investigated, and safe and effective stimulation guidelines have been identified for research studies and in clinical practice for tDCS applications involving human subjects. In the several hundred studies conducted on humans using tDCS, the only side effects that have been reported when proper guidelines are followed are temporary tingling, itching, mild headache, or skin redness under the electrodes in some subjects.

In conclusion, the tDCS stimulation parameters in this study are identical to the most common in the literature and have been proven to be exceptionally safe and well-tolerated. ***Please let us know immediately if you develop any skin pain or discomfort during tDCS.*** We will monitor you during stimulation and will stop the procedure if any problem develops. ***You may ask to stop the procedure at any time.*** Any effects of tDCS should wear off within 60-90 minutes after the current is stopped.

Risks of TMS

TMS is a safe, non-invasive brain stimulation technique that can be used for both diagnostic and therapeutic procedures. The single pulse TMS techniques that will be performed in this study has been used extensively in thousands of research studies and on tens of thousands of subjects in the United States and around the world. Single paired pulse TMS technique is considered very safe when accepted guidelines are followed and no long-term risks have been reported involving the use of single and paired-pulse TMS. For most people, the single pulse stimulation is not painful, but

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occasionally slight discomfort or headache can occur. The headaches go away quickly with nonprescription medication. TMS produces a loud clicking sound when a current is passed through the stimulation coil. This click can result in ringing in the ear and temporary shifts in your ability to determine the pitch and loudness of sounds, if no protection is used. In order to prevent this possible side effect, we will ask you to wear earplugs that block the noise of the TMS. Hearing damage is possible and one subject suffered permanent hearing damage when hearing protection fell out, although this was done using repetitive TMS (rTMS). This ***study does NOT include rTMS or paired pulse TMS and only single pulse TMS will be employed in this study (see below).*** Animal and human studies have shown that earplugs or headphones can effectively prevent the risk of hearing disturbance due to TMS. Therefore, you will be fitted with earplugs during TMS. ***If you find the procedure too uncomfortable, you may discontinue it at any time***.

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 (dental work such as fillings and similar procedures do not pose a risk and are acceptable). Please inform the investigators if you have any of these or known hearing loss. ***If metal is present or you have an implanted device or metal object that is not safe for TMS, you will not be allowed to participate.***

In general, the risks associated with TMS are very minimal but research has shown that there is a very small risk of seizures if repetitive TMS (rTMS) is done with very intense, high frequency stimulation or with trains of stimulation separated by a second or less. ***Such intensity, frequency and repetition rate will not be used in this study as the study does NOT include rTMS and only single pulse TMS method will be employed.*** Finally, there is no medical risk associated with the surface EMG recordings of the muscle responses to TMS.

<u>Risks of Performing Motor Tasks</u>

Generally, the procedures outlined for measuring force and muscle activity during the motor tasks are safe. Nevertheless, there is potential for injury (muscle strain), resulting from the maximal contractions. There is a 0.01% chance of death (in people who have heart problems), a 0.02% risk of cardiac arrhythmias that would require you to go the hospital (in people with heart problems), and a risk of an increase or decrease in blood pressure.

All contractions are voluntary and you can stop immediately if they experience any slight pain or discomfort. Following participation, you may experience some muscle soreness. Muscle soreness tends to be more common for individuals who have not exercised recently. Other risk factors may include increased feelings of anxiety and/or stress induced by the experiment, which can lead to an increase in heart rate and blood pressure. The EMG electrodes that will be used to measure muscle activity could

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potentially cause skin irritation after removal. Furthermore, your skin will need to be shaved prior to placing the electrodes, which can also cause irritation.

General Risk

Even though the risk is minimal, there is a risk for breach of confidentiality. Your data will be coded to prevent any link to your identity, and any identifying material will be locked in a secure filing cabinet. Furthermore, the potential physical risks of participating in the proposed experiments are reasonably small. The motor performance tasks have been used previously by the members of the investigative team without complication.

ARE THERE ANY BENEFITS FROM TAKING PART IN THIS STUDY?
There may be no direct benefit to you associated with this research. This study is designed for the researcher to learn more about mobility problems and fatigue in persons with MS. This study is not designed to treat any illness or to improve your health.

DO I HAVE TO TAKE PART IN THE STUDY?
Your participation in this research is voluntary. If you decide to participate in the study, you may withdraw your consent and stop participating at any time.

WHAT WILL IT COST ME TO PARTICIPATE?
Other than transport to and from the lab, your participation should incur no costs.

WHO WILL SEE THE INFORMATION THAT I GIVE?
We will keep private all research records that identify you, to the extent allowed by law. Your information will be combined with information from other people taking part in the study. When we write about the study to share with other researchers, we will write about the combined information we have gathered. You will not be identified in these written materials. We may publish the results of this study; however, we will keep your name and other identifying information private.

We will make every effort to prevent anyone who is not on the research team from knowing that you gave us information, or what that information is. For example, your name will be kept separate from your research records and these two things will be stored in different places under lock and key. You should know, however, that there are some circumstances in which we may have to show your information to other people. In addition, for funded studies, the CSU financial management team may also request an audit of research expenditures. For financial audits, only the fact that you participated would be shared, not any research data. We may be asked to share the research files with the CSU Institutional Review Board ethics committee for auditing purposes, if necessary.

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CAN MY TAKING PART IN THE STUDY END EARLY?
If you fail to show up to your visits you may be removed from the study.

WILL I RECEIVE ANY COMPENSATION FOR TAKING PART IN THIS STUDY?
Yes, once you have completed the study you will receive $20.

WHAT HAPPENS IF I AM INJURED BECAUSE OF THE RESEARCH?
The Colorado Governmental Immunity Act determines and may limit Colorado State University's legal responsibility if an injury happens because of this study. Claims against the University must be filed within 180 days of the injury. The research team will not cover any injury resulting in this study. You and/or your health insurance will be responsible for paying for any study-related injury.

WHAT IF I HAVE QUESTIONS?
Before you decide whether to accept this invitation to take part in the study, please ask any questions that might come to mind now. Later, if you have questions about the study, you can contact the investigator, Dr. Thorsten Rudroff, via phone 970-491-8655 or email: Thorsten.rudroff@colostate.edu. If you have any questions about your rights as a volunteer in this research, contact the CSU IRB at: RICRO_IRB@mail.colostate.edu; 970-491-1553. We will give you a copy of this consent form to take with you.

WHAT ELSE DO I NEED TO KNOW?

A description of this clinical trial will be available on http://www.ClincialTrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at anytime.

FUTURE STUDIES:
Would you like to be contacted for future studies that you may be eligible for? Please initial: _____Yes _____No

Your signature acknowledges that you have read the information stated and willingly sign this consent form. Your signature also acknowledges that you have received, on the date signed, a copy of this document containing __7__ pages.

_____ _____
Signature of person agreeing to take part in the study Date

_____ _____
Printed name of person agreeing to take part in the study Time of Day

_____ _____

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APPROVED: 9/15/2017 EXPIRES: 9/14/2018

Name of person providing information to participant Date

_____

Signature of Research Staff

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Consent to Participate in a Research Study
Colorado State University

TITLE OF STUDY: Can transcranial direct current stimulation (tDCS) improve ambulation and fatigue resistance in people with MS?

PRINCIPAL INVESTIGATORS:
The principal investigator is a researcher in the Department of Health and Exercise Science at Colorado State University:

Thorsten Rudroff, Ph.D., FACSM
HES-INPL@mail.ColoState.EDU
970-491-8655

WHY AM I BEING INVITED TO TAKE PART IN THIS RESEARCH?
You are an adult aged between 30 and 60 years of age, and you were diagnosed with Multiple Sclerosis.

WHO IS DOING THE STUDY?
Dr. Rudroff and his graduate students John Kindred, Nathan Ketelhut, and Felix Proessl are performing the study in the Integrative Neurophysiology Laboratory.

WHAT IS THE PURPOSE OF THIS STUDY?
The purpose of this study is to determine if a single session of tDCS can increase the muscle strength of the more affected leg in people with MS.

WHERE IS THE STUDY GOING TO TAKE PLACE AND HOW LONG WILL IT LAST?
The study will take place in the Integrative Neurophysiology Laboratory in the Department of Health and Exercise Science, on the Colorado State University campus. The study will run for approximately 12 months. You will take part in the study for approximately a total of 3 hours over the space of two weeks.

WHAT WILL I BE ASKED TO DO?
You will be asked to participate in two sessions on two different days separated by no less than 7 days. Each visit will last approximately 90min.

If you participate in this study you will perform strength tests of your leg muscles in association with 1 of 2 intervention protocols involving tDCS application (BEFORE and SHAM) with each intervention protocol being performed in a separate session on a different day. Thus, in one session you will receive tDCS before the strength test, whereas in another session you will receive sham tDCS before the strength test.

Upon arrival to the INPL the investigators will explain the protocol procedures and receive signed informed consent from you.

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- *Questionnaires:* You will fill out to questionnaires relating to fatigue and depression.
- *Body Composition*: We will perform a Dual-Energy X-Ray Absorptiometry (DXA) scan on you. A very small amount of X-Rays will pass through your body and allow us to measure the amount of muscle, fat, and bone you have.
- *Leg Strength:* The maximal strength of each leg will be measured by having you perform a series of maximal effort knee extension, knee flexion, plantar/dorsi-flexion trials. This will be performed one leg at a time up to five times. The activity of your muscles will be measured during this task by placing a series of electrodes on the skin of your legs.
- *6 Minute Walk Test:* After completion of the strength testing we will see how far you can walk in 6 minutes. You will be allowed to stop and rest as needed.

tDCS is a non-invasive technique in which a very weak electrical current is applied to the head in order to stimulate the brain. For tDCS, we will place rubber electrodes soaked in salt water or electrode gel over your scalp and forehead. Therefore, one of the electrodes will be placed over your hair, but no additional substances will be put in your hair and no additional preparation of the hair will be conducted. The electrodes will be held in place with a head band. A small current will be passed between the electrodes. You may feel some tingling under the electrodes when the current is first turned on. The stimulation will last 10 minutes.

To find the right location of electrode on your head we will use transcranial magnetic stimulation (TMS). For application of TMS, a wire coil is held on the scalp. A brief electrical current is passed through the coil and creates a magnetic pulse that stimulates the brain. You will hear a click and may feel a pulling sensation on the skin under the coil and there may be a twitch in muscles of the face, arm or leg. During the stimulation, you will be at rest. You will wear a shower cap during the TMS testing and marks will be made on the cap to denote positioning of the coil.

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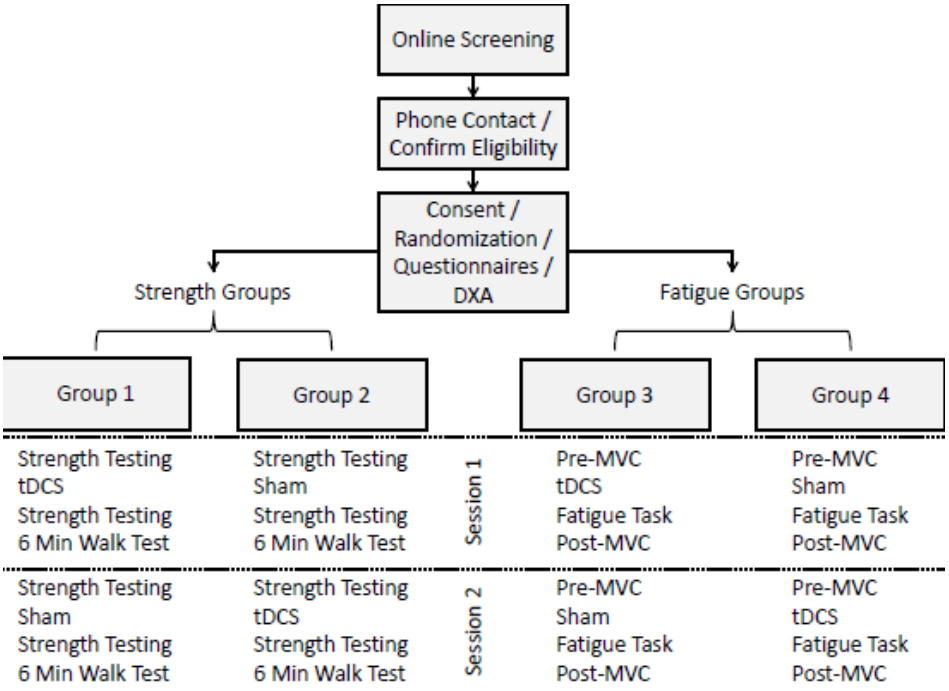

ARE THERE

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- Medical diagnosis or condition that makes participating in exercise training dangerous, such as major renal, pulmonary, hepatic, cardiac, gastrointestinal, HIV, cancer (other than treated basal cell cancer), other neurological disorders, or pregnancy
- History of heart attack or current diagnosis of cardiovascular disease
- History of seizure disorders (or on medications known to lower seizure threshold)
- Hydrocephalus (buildup of fluid in the brain)
- Alcohol dependence or abuse (>2 drinks/day), or present history (last six months) of drug abuse
- History of significant traumatic brain injury or hydrocephalus
- Pregnancy
- Recent hospitalization (within the last 3 months) or enforced bed rest/sedentary state.
- Presence of metal is present or implanted device or metal object that is not safe for TMS.
- Presence of holes or fissures of the cranial bones

WHAT ARE THE POSSIBLE RISKS AND DISCOMFORTS?

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The risks associated with the DEXA are very low. The maximum radiation dose you will receive in this study is less than 1/1000th of the federal and state occupational whole body dose limit allowed to radiation workers (5,000 mrem) (mrem is a unit used to measure radiation dosage). Put another way, the maximum dose from any scan we utilize with this DEXA ranges from 1.2 mrem (Whole body scan) to 12.2 mrem (for several of the regional scans, such as lumbar, femur, and forearm scans). The average annual background radiation you already receive is at least 620 mrem/year. The more radiation you receive over the course of your life, the more the risk increases of developing a fatal cancer or inducing changes in genes. The radiation in this scan is not expected to significantly increase these risks, but the exact increase in such risks is not known. There are no discomforts associated with this procedure.

Risks of tDCS

tDCS has been conducted on humans and animals for many years and no evidence has emerged to suggest that it is harmful or has ever induced a serious side effect. However, the safety of tDCS is dependent on current strength, electrode size, and stimulation duration. Accordingly, these parameters have been investigated, and safe and effective stimulation guidelines have been identified for research studies and in clinical practice for tDCS applications involving human subjects. In the several hundred studies conducted on humans using tDCS, the only side effects that have been reported when proper guidelines are followed are temporary tingling, itching, mild headache, or skin redness under the electrodes in some subjects.

In conclusion, the tDCS stimulation parameters in this study are identical to the most common in the literature and have been proven to be exceptionally safe and well-tolerated. ***Please let us know immediately if you develop any skin pain or discomfort during tDCS.*** We will monitor you during stimulation and will stop the procedure if any problem develops. ***You may ask to stop the procedure at any time.*** Any effects of tDCS should wear off within 60-90 minutes after the current is stopped.

Risks of TMS

TMS is a safe, non-invasive brain stimulation technique that can be used for both diagnostic and therapeutic procedures. The single pulse TMS techniques that will be performed in this study has been used extensively in thousands of research studies and on tens of thousands of subjects in the United States and around the world. Single paired pulse TMS technique is considered very safe when accepted guidelines are followed and no long-term risks have been reported involving the use of single and paired-pulse TMS. For most people, the single pulse stimulation is not painful, but occasionally slight discomfort or headache can occur. The headaches go away quickly with nonprescription medication. TMS produces a loud clicking sound when a current is passed through the stimulation coil. This click can result in ringing in the ear and

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temporary shifts in your ability to determine the pitch and loudness of sounds, if no protection is used. In order to prevent this possible side effect, we will ask you to wear earplugs that block the noise of the TMS. Hearing damage is possible and one subject suffered permanent hearing damage when hearing protection fell out, although this was done using repetitive TMS (rTMS). This ***study does NOT include rTMS or paired pulse TMS and only single pulse TMS will be employed in this study (see below).*** Animal and human studies have shown that earplugs or headphones can effectively prevent the risk of hearing disturbance due to TMS. Therefore, you will be fitted with earplugs during TMS. ***If you find the procedure too uncomfortable, you may discontinue it at any time***.

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 (dental work such as fillings and similar procedures do not pose a risk and are acceptable). Please inform the investigators if you have any of these or known hearing loss. ***If metal is present or you have an implanted device or metal object that is not safe for TMS, you will not be allowed to participate.***

In general, the risks associated with TMS are very minimal but research has shown that there is a very small risk of seizures if repetitive TMS (rTMS) is done with very intense, high frequency stimulation or with trains of stimulation separated by a second or less. ***Such intensity, frequency and repetition rate will not be used in this study as the study does NOT include rTMS and only single pulse TMS method will be employed.*** Finally, there is no medical risk associated with the surface EMG recordings of the muscle responses to TMS.

Risks of Performing Motor Tasks

Generally, the procedures outlined for measuring force and muscle activity during the motor tasks are safe. Nevertheless, there is potential for injury (muscle strain), resulting from the maximal contractions. There is a 0.01% chance of death (in people who have heart problems), a 0.02% risk of cardiac arrhythmias that would require you to go the hospital (in people with heart problems), and a risk of an increase or decrease in blood pressure.

All contractions are voluntary and you can stop immediately if they experience any slight pain or discomfort. Following participation, you may experience some muscle soreness. Muscle soreness tends to be more common for individuals who have not exercised recently. Other risk factors may include increased feelings of anxiety and/or stress induced by the experiment, which can lead to an increase in heart rate and blood pressure. The EMG electrodes that will be used to measure muscle activity could potentially cause skin irritation after removal. Furthermore, your skin will need to be shaved prior to placing the electrodes, which can also cause irritation.

General Risk

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Even though the risk is minimal, there is a risk for breach of confidentiality. Your data will be coded to prevent any link to your identity, and any identifying material will be locked in a secure filing cabinet. Furthermore, the potential physical risks of participating in the proposed experiments are reasonably small. The motor performance tasks have been used previously by the members of the investigative team without complication.

ARE THERE ANY BENEFITS FROM TAKING PART IN THIS STUDY?
There may be no direct benefit to you associated with this research. This study is designed for the researcher to learn more about mobility problems and fatigue in persons with MS. This study is not designed to treat any illness or to improve your health.

DO I HAVE TO TAKE PART IN THE STUDY?
Your participation in this research is voluntary. If you decide to participate in the study, you may withdraw your consent and stop participating at any time.

WHAT WILL IT COST ME TO PARTICIPATE?
Other than transport to and from the lab, your participation should incur no costs.

WHO WILL SEE THE INFORMATION THAT I GIVE?
We will keep private all research records that identify you, to the extent allowed by law. Your information will be combined with information from other people taking part in the study. When we write about the study to share with other researchers, we will write about the combined information we have gathered. You will not be identified in these written materials. We may publish the results of this study; however, we will keep your name and other identifying information private.

We will make every effort to prevent anyone who is not on the research team from knowing that you gave us information, or what that information is. For example, your name will be kept separate from your research records and these two things will be stored in different places under lock and key. You should know, however, that there are some circumstances in which we may have to show your information to other people. We may be asked to share the research files with the CSU Institutional Review Board ethics committee for auditing purposes, if necessary.

CAN MY TAKING PART IN THE STUDY END EARLY?
If you fail to show up to your visits you may be removed from the study.

WILL I RECEIVE ANY COMPENSATION FOR TAKING PART IN THIS STUDY?
There is no compensation for this study.

WHAT HAPPENS IF I AM INJURED BECAUSE OF THE RESEARCH?

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The Colorado Governmental Immunity Act determines and may limit Colorado State University's legal responsibility if an injury happens because of this study. Claims against the University must be filed within 180 days of the injury. The research team will not cover any injury resulting in this study. You and/or your health insurance will be responsible for paying for any study-related injury.

WHAT IF I HAVE QUESTIONS?

Before you decide whether to accept this invitation to take part in the study, please ask any questions that might come to mind now. Later, if you have questions about the study, you can contact the investigator, Dr. Thorsten Rudroff, via phone 970-491-8655 or email: Thorsten.rudroff@colostate.edu. If you have any questions about your rights as a volunteer in this research, contact the CSU IRB at: RICRO_IRB@mail.colostate.edu; 970-491-1553. We will give you a copy of this consent form to take with you.

WHAT ELSE DO I NEED TO KNOW?

A description of this clinical trial will be available on http://www.ClincialTrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at anytime.

FUTURE STUDIES:

Would you like to be contacted for future studies that you may be eligible for? Please initial: _____Yes _____No

Your signature acknowledges that you have read the information stated and willingly sign this consent form. Your signature also acknowledges that you have received, on the date signed, a copy of this document containing __7__ pages.

_____ _____

Signature of person agreeing to take part in the study Date

_____ _____

Printed name of person agreeing to take part in the study Time of Day

_____ _____

Name of person providing information to participant Date

_____

Signature of Research Staff

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APPROVED: 9/15/2017 * EXPIRES: 9/14/2018

Title: Can transcranial direct current stimulation improve ambulation and fatigue resistance in people with MS?
NCT #: NCT02987621
Document date: 08/24/2017

Statistical analysis:

Separated by a minimum of 7 days, participants performed experimental protocol twice once with tDCS and once with Sham in a counterbalanced order. A repeated measures ANOVA (condition x time) and paired t-tests were used to compare Sham vs. tDCS. Data are reported as means (tDCS vs Sham) plus or minus the standard deviations.