Cerebellar tDCS, gait and balance training in PwMS

PI: Alexandra Fietsam
IRB ID #: 201912430

Project Details

I. Project Introduction

I.1 ***Project to be reviewed by:***
IRB-01

I.2 ***Project Title:***
The effects of 4 mA cerebellar transcranial direct current stimulation combined with gait and balance training in people with multiple sclerosis

I.3 ***Short Title (optional):***
Cerebellar tDCS, gait and balance training in PwMS

I.4 ***Provide a short summary of the purpose and procedures of the study proposed in this IRB application.***

- ***DO NOT include information on studies not proposed in this application.***
- ***Use LAY terminology only. This must be easily understandable by IRB community members and nonscientists.***
- ***DO NOT cut and paste technical abstracts from funding applications that may not be understood by a general audience.***

The purpose of this study is to investigate the effects of cerebellar transcranial direct current stimulation (tDCS) combined with gait or balance training on glucose uptake in the leg muscles as well as gait and balance performance. We will conduct tDCS or SHAM followed by balance or gait training over 9 days. We will evaluate gait and balance with well-established functional tasks and changes in glucose uptake with PET-FDG imaging.

I.5 ***Specify your research question(s), study aims or hypotheses (do not indicate "see protocol")***
Our research question is whether tDCS combined with gait and balance training can improve gait and balance performance as well as increase glucose uptake symmetry in the leg muscles of people with multiple sclerosis. We hypothesize that gait, balance, and glucose uptake symmetry will improve in both groups that received training (gait or balance) combined with tDCS compared to the groups that only receive training (sham tDCS). Moreover, we hypothesize that the greatest improvements will be seen in the gait and tDCS group.

I.6 ***Background and significance and/or Preliminary studies related to this project. (do not indicate "see protocol")***
Many people with multiple sclerosis (PwMS) have decreased balance (1,2) and postural control(3), gait deficits(4), and a high frequency of falls(5). High fall rates and mobility impairments pose a significant risk to the independence and quality of life of PwMS(8,9). Therefore, effective interventions to improve gait, balance and postural control are urgently needed to decrease the frequency of falls in PwMS. Gait and balance training has been demonstrated to significantly improve postural control and gait in PwMS (10,11). However, a standardized protocol for balance interventions has not been established. However, the cumulative evidence shows that only small improvements in walking ability are associated with exercise training short-term and the long-term effects are ambiguous (13). One possible treatment modality to amplify the effects of gait balance training is transcranial direct current stimulation (tDCS), a non-invasive means to increase cortical excitability and potentially prime the brain for task specific learning(14). The cerebellum plays a vital role in balance and posture and may be an important target structure for tDCS studies seeking to improve gait and balance (14-17). Studies have shown that anodal cerebellar tDCS is effective in improving balance control in older adults with high fall risk(18) and patients with chronic stroke(19). However, the most effective tDCS intensity and the duration of the effects on gait balance control has not been established(20,21).

I.7 ***Literature cited / references (if attaching a grant or protocol enter N/A).***

1. Martin, C. L., Phillips, B. A., Kilpatrick, T. J. et al. Gait and balance impairment in early multiple sclerosis in the absence of clinical disability. Mult Scler 12, 620-628, doi:10.1177/1352458506070658 (2006).
2. Soyuer, F., Mirza, M. & Erkorkmaz, U. Balance performance in three forms of multiple sclerosis. Neurol Res 28, 555-562, doi:10.1179/016164105X49373 (2006).
3. Cameron, M. H. & Lord, S. Postural control in multiple sclerosis: implications for fall prevention. Curr Neurol Neurosci Rep 10, 407-412, doi:10.1007/s11910-010-0128-0 (2010).
4. Comber, L., Galvin, R. & Coote, S. Gait deficits in people with multiple sclerosis: A systematic review and meta-analysis. Gait Posture 51, 25-35, doi:10.1016/j.gaitpost.2016.09.026 (2017).
5. Gianni, C., Prosperini, L., Jonsdottir, J. et al. A systematic review of factors associated with accidental falls in people with multiple sclerosis: a meta-analytic approach. Clin Rehabil 28, 704-716, doi:10.1177/0269215513517575 (2014).
6. Chua, M. C., Hyngstrom, A. S., Ng, A. V. et al. Movement strategies for maintaining standing balance during arm tracking in people with multiple sclerosis. J Neurophysiol 112, 1656-1666, doi:10.1152/jn.00598.2013 (2014).
7. Hwang, S., Tae, K., Sohn, R. et al. The balance recovery mechanisms against unexpected forward perturbation. Ann Biomed Eng 37, 1629-1637, doi:10.1007/s10439-009-9717-y (2009).
8. Larocca, N. G. Impact of walking impairment in multiple sclerosis: perspectives of patients and care partners. Patient 4, 189-201, doi:10.2165/11591150-000000000-00000 (2011).
9. Coleman, C. I., Sidovar, M. F., Roberts, M. S. et al. Impact of mobility impairment on indirect costs and health-related quality of life in multiple sclerosis. PLoS One 8, e54756, doi:10.1371/journal.pone.0054756 (2013).
10. Hebert, J. R., Corboy, J. R., Manago, M. M. et al. Effects of vestibular rehabilitation on multiple sclerosis-related fatigue and upright postural control: a randomized controlled trial. Phys Ther 91, 1166-1183, doi:10.2522/ptj.20100399 (2011).
11. Jonsdottir, J., Lencioni, T., Gervasoni, E. et al. Improved Gait of Persons With Multiple Sclerosis After Rehabilitation: Effects on Lower Limb Muscle Synergies, Push-Off, and Toe-Clearance. Front Neurol 11, 668, doi:10.3389/fneur.2020.00668 (2020).
12. Baird, J. F., Sandroff, B. M. & Motl, R. W. Therapies for mobility disability in persons with multiple sclerosis. Expert review of neurotherapeutics 18, 493-502, doi:10.1080/14737175.2018.1478289 (2018).
13. Stagg, C. J., Jayaram, G., Pastor, D. et al. Polarity and timing-dependent effects of transcranial direct current stimulation in explicit motor learning. Neuropsychologia 49, 800-804, doi:10.1016/j.neuropsychologia.2011.02.009 (2011).
14. Taube, W., Mouthon, M., Leukel, C. et al. Brain activity during observation and motor imagery of different balance tasks: an fMRI study. Cortex 64, 102-114, doi:10.1016/j.cortex.2014.09.022 (2015).
15. Taubert, M., Lohmann, G., Margulies, D. S. et al. Long-term effects of motor training on resting-state networks and underlying brain structure. Neuroimage 57, 1492-1498, doi:10.1016/j.neuroimage.2011.05.078 (2011).
16. Ouchi, Y., Okada, H., Yoshikawa, E. et al. Brain activation during maintenance of standing postures in humans. Brain 122 (Pt 2), 329-338, doi:10.1093/brain/122.2.329 (1999).
17. Surgent, O. J., Dadalko, O. I., Pickett, K. A. et al. Balance and the brain: A review of structural brain correlates of postural balance and balance training in humans. Gait Posture 71, 245-252, doi:10.1016/j.gaitpost.2019.05.011 (2019).
18. Yosephi, M. H., Ehsani, F., Zoghi, M. et al. Multi-session anodal tDCS enhances the effects of postural training on balance and postural stability in older adults with high fall risk: Primary motor cortex versus cerebellar stimulation. Brain Stimul 11, 1239-1250, doi:10.1016/j.brs.2018.07.044 (2018).
19. Zandvliet, S. B., Meskers, C. G. M., Kwakkel, G. et al. Short-Term Effects of Cerebellar tDCS on Standing Balance Performance in Patients with Chronic Stroke and Healthy Age-Matched Elderly. Cerebellum 17, 575-589, doi:10.1007/s12311-018-0939-0 (2018).
20. Nitsche, M. A. & Bikson, M. Extending the parameter range for tDCS: Safety and tolerability of 4 mA stimulation. Brain Stimul 10, 541-542, doi:10.1016/j.brs.2017.03.002 (2017).
21. Esmaeilpour, Z., Marangolo, P., Hampstead, B. M. et al. Incomplete evidence that increasing current intensity of tDCS boosts outcomes. Brain Stimul 11, 310-321, doi:10.1016/j.brs.2017.12.002 (2018).

II. Research Team

II.1 ***Principal Investigator***

Name	E-mail	College
Alexandra Fietsam	alexandra-fietsam@uiowa.edu	Inst Clinical & Translational

II.2 ***Team Members***

UI Team Members

Name	E-mail	College	Contact	Key Prsn	UI COI	VAMC COI	Consent Process Involvement	Deactivated
Alexandra Fietsam, MS	alexandra-fietsam@uiowa.edu	Inst Clinical & Translational	Yes	Yes	No		Yes	No
David Bushnell, MD	david-bushnell@uiowa.edu	Carver College of Medicine	Yes	Yes	No		No	No
Justin Deters, MS	justin-deters@uiowa.edu	Graduate College	Yes	Yes	No		Yes	No
Lisa Dunnwald, MPH	lisa-dunnwald@uiowa.edu	University Hospitals	Yes	Yes	No		No	No
Christine Gill, MD	christine-gill@uiowa.edu	Carver College of Medicine	No	Yes	No		Yes	No
Michael Graham, MD, PHD	michael-graham@uiowa.edu	Carver College of Medicine	Yes	Yes	No		No	No
John Kamholz, MD, PhD, MD	john-kamholz@uiowa.edu	Carver College of Medicine	Yes	Yes	No		Yes	No
Shannon Lehman, BA	shannon-lehman@uiowa.edu	University Hospitals	Yes	Yes	No		No	No
Parren McNeely, MD	parren-mcneely@uiowa.edu	Carver College of Medicine	Yes	Yes	No		No	No
Yusuf Menda, MD	yusuf-menda@uiowa.edu	Carver College of Medicine	Yes	Yes	No		No	No
Janet Pollard, MD	janet-pollard@uiowa.edu	Carver College of Medicine	Yes	Yes	No		No	No
Laura Ponto, PHD	laura-ponto@uiowa.edu	Carver College of Medicine	Yes	Yes	No		No	No
Thorsten Rudroff, PHD	thorsten-rudroff@uiowa.edu	College Lib Arts and Sciences	Yes	Yes	No		Yes	No

Non-UI Team Members

Name	Institution	Location	FWA	Role	DHHS Contact	Key Prsn	UI COI	VAMC COI	Consent Process Involvement	Email

Nothing found to display.

II.3 ***The Principal Investigator of this study is:***
Graduate student

II.3.a ***Select the mentor or faculty advisor:***
Thorsten Rudroff

II.6 ***Identify the key personnel. The system will automatically designate the PI and all faculty members on the project as "key personnel." For information about other team members who should be designated as "key personnel" please click on the help information.***

Name	Is Key Personnel
Alexandra Fietsam, MS	Yes
David Bushnell, MD	Yes

Justin Deters, MS	Yes
Lisa Dunnwald, MPH	Yes
Christine Gill, MD	Yes
Michael Graham, MD, PHD	Yes
John Kamholz, MD, PhD, MD	Yes
Shannon Lehman, BA	Yes
Parren McNeely, MD	Yes
Yusuf Menda, MD	Yes
Janet Pollard, MD	Yes
Laura Ponto, PHD	Yes
Thorsten Rudroff, PHD	Yes

II.5 ***Select research team member who is the primary contact for study participants.***
Alexandra Fietsam

III. Funding/Other Support

III.1 ***Funding Sources***

Source Entered as Text	DSP Link	Type	Source Grant Title	Name of PI on Grant
Source is entered as text no * new source name		Departmental / PI Discretionary		

III.3 ***Does any member of the research team have a financial conflict of interest related to this project according to the Conflict of Interest in Research policy? If yes, please indicate which members below.***

Name	Has Conflict of Interest
Alexandra Fietsam, MS	No
David Bushnell, MD	No
Justin Deters, MS	No
Lisa Dunnwald, MPH	No
Christine Gill, MD	No
Michael Graham, MD, PHD	No
John Kamholz, MD, PhD, MD	No
Shannon Lehman, BA	No
Parren McNeely, MD	No
Yusuf Menda, MD	No
Janet Pollard, MD	No
Laura Ponto, PHD	No
Thorsten Rudroff, PHD	No

IV. Project Type

IV.1 ***Do you want the IRB to give this project***
Regular (expedited or full board) review

IV.2 ***Enter the date you will be ready to begin screening subjects/collecting data for this project. (If you do not have a specified date, add "upon IRB approval")***
upon IRB approval

IV.3 ***Are you requesting a waiver of informed consent/authorization (subjects will not be given any oral or written information about the study)?***
No

V. Other Committee Review

V.1 ***Does this project involve any substance ingested, injected, or applied to the body?***

- ***Do not answer yes, if the involvement includes a device, wire, or instrument***

Yes

V.1.a ***What is/are the substance(s):***
[18F]flurodeoxyglucose (18F-FDG)

V.1.b ***Are any of these substances defined as a Schedule I - V Controlled Substance?***
No

V.2 ***Are any contrast agents used for any purpose in this study?***
No

V.4 ***Are all drugs or substances in this study being used within the FDA approved population (i.e., children, adults)?***
Yes

V.5 ***Are all drugs or substances in this study being used within the FDA approved indication (i.e., disease, condition)?***
No

V.6 ***Are all drugs or substances in this study being used within the FDA approved dose?***
Yes

V.7 ***Are all drugs or substances in this study being used within the FDA approved route of administration?***
Yes

V.8 ***Drugs used in study that are not FDA approved for the population, indication, dose, or route of administration***

Fludeoxyglucose F 18 Injection (FDG)

Name of Sponsor	UIHC - PET Imaging Center
Investigator's Brochure Version	N/A
Investigator's Brochure Date	N/A
Who is supplying the drug	
Who is dispensing the drug	
Planned Use in this Study	
Condition/Disease Indication(s)	Evaluation of glucose metabolism in the skeletal muscle, spinal cord and brain of MS patients after treadmill walking
Subject Population	Adult MS patients
Dose(s)	10 mCi as an intravenous injection
Administration	Intravenous
Dosing Regimen	Single dose per imaging session
FDA Approved Use	
Approved Condition/Disease Indication(s)	Fludeoxyglucose F18 Injection is indicated for positron emission tomography (PET) imaging in the following settings: • Oncology: For assessment of abnormal glucose metabolism to assist in the evaluation of malignancy. • Cardiology: For the identification of left ventricular myocardium with residual glucose metabolism. • Neurology: For the identification of regions of abnormal glucose metabolism

Approved Patient Population	Adults and pediatric patients
Approved Dose(s)	5-10 mCi as an intravenous injection
Approved Administration	Intravenous
Approved Dosing Regimen	Single dose per imaging session
Is this study intended to be reported to the FDA as a well-controlled study in support of a new indication or a significant change in the labeling for this product?	No
Is this study intended to support a significant change in the advertising for this product?	No
Does this planned use of the product in this study, taking into consideration the route of administration, the dosage level, and the subject population, significantly increase the risk (or decrease the acceptability of the risk) associated with the use of this product?	No
Rationale:	Skeletal muscle uptake is generally a nuisance factor in oncology and brain imaging studies. However, this uptake has been used to evaluate muscle function. The following reference is just one example. Shiozawa H, et al. Evaluation of muscle activity just after straight leg raising exercise by using 18FDG-PET. Journal of Orthopaedic Science. 2018; 23: 328e333

V.9 ***Will any subject be asked to undergo a diagnostic radiation procedure (including radiographic, nuclear medicine, DEXA)?***
Yes

V.10 ***Are all diagnostic radiation procedures routine, standard, clinical procedures?***
Yes

V.11 ***Will all subjects who receive the diagnostic radiation procedure(s) require the exact same procedure for clinical purposes?***
No

V.14 ***Will any subject be asked to undergo a radiation therapy procedure (including external beam therapy, brachytherapy, or nuclear medicine therapy)?***
No

V.20 ***Does this project involve the deliberate transfer of recombinant or synthetic nucleic acid molecules, or DNA or RNA derived from recombinant or synthetic nucleic acid molecules, into one or more human research participant?***
No

V.21 ***Will any portion of this project be conducted in the CRU, or does it use any CRU resources?***
No

V.22 ***Will this project use:***

- ***any resource/patients of the Holden Comprehensive Cancer Center***
- ***involve treatment, detection, supportive care, or prevention of cancer***

No

V.25.a ***Will the study involve <u>any</u> of the following activity at UI Health Care, even if subjects or their insurance will not be***

billed for the item or service, and regardless of the study funding source (including studies with departmental or no funding)?

- ***Procedures, tests, examinations, hospitalizations, use of Pathology services, use of clinic facilities or clinical equipment, or any patient care services, including services conducted in the Clinical Research Unit; or***
- ***Physician services or services provided by non-physicians who are credentialed to bill (ARNPs, Physician Assistants, etc.)***

Yes

V.25.b ***Will there be any procedures or services that may happen as part of a subject's regular medical care and as part of the study?***
No

V.25.c ***Will any study equipment or devices be supplied by a study sponsor?***
No

V.25.e ***Is there or will there be an internal budget for this study?***
Yes

V.25.f ***Is there or will there be an external budget for this study?***
No

V.26 ***The study involves Department of Nursing Services and Patient Care nursing, nursing resources or evaluates nursing practices at UI Health Care.***
No

VI. Subjects

VI.1 ***How many adult subjects do you expect to consent or enroll for this project?***
48

VI.2 ***What is the age of the youngest adult subject?***
18.0

VI.3 ***What is the age of the oldest adult subject?***
75.0

VI.4 ***What is the percentage of adult male subjects?***
30

VI.5 ***What is the percentage of adult female subjects?***
70

VI.6 ***How many minor subjects do you expect to consent or enroll for this project?***
0

VI.13 ***Describe EACH of your subject populations***

- ***Include description of any control group(s)***
- ***Specify the Inclusion/Exclusion criteria for EACH group***

Inclusion criteria: medically diagnosed with relasping-remitting multiple sclerosis, 18-75 years of age, moderate disability (score of 2-6 on the Patient Determined Disease Scale [PPDS]), self-reported differences in function between legs, able to walk on a treadmill for at least 20 mins, and not taking any psychoactive medication.

Exclusion criteria: relapse within the last 60 days, have changed disease modifying medications in the last 45 days, are currently pregnant, have a concurrent neurological or neuromuscular disease, have been hospitalized within the last 90

days, have any contraindications for the tDCS device (i.e., pacemakers or metal implants), or are unable to understand/sign the consent form.

VI.14 ***Provide an estimate of the total number of subjects that would be eligible for inclusion in each of your study populations (include your control population if applicable)***
48

VI.15 ***Describe how you will have access to each of your study populations in sufficient number to meet your recruitment goals.***
We will generate a list of MS patients from our population seen in the Neurology clinic whose diagnosis is listed as MS in Epic. Furthermore, we will distribute flyers around the UIowa clinics and hospital.

VI.16 ***Do you plan to recruit/enroll non-English speaking people?***
No

VI.18 ***Do you propose to enroll any of the following in this study as subjects?***

- ***Employee of the PI or employee of a research team member***
- ***Individual supervised by PI or supervised by member of research team***
- ***Individual subordinate to the PI or subordinate to any member of the research team***
- ***Student or trainee under the direction of the PI or under the direction of a member of the research team***

No

VI.20 ***Will subjects provide any information about their relatives?***
No

VI.23 ***Will anyone (other than the subject) provide you with information about the subject (e.g. proxy interviews)?***
No

VI.26 ***Is this project about pregnant women?***
No

VI.27 ***Will this project involve fetuses?***
No

VI.28 ***Does this project involve adult subjects who may be incompetent or have limited decision-making capacity on initial enrollment into the study?***
No

VI.32 ***Does this project involve subjects whose capacity to consent may change over the course of the study?***
No

VI.37 ***Does this project involve prisoners as subjects?***
No

VII.A. Project Description (A)

VII.A.1 ***Where will project procedures take place (check all that apply)?***

- UIHC - UIHC - Multiple Sclerosis Clinic, Department of Neurology; PET Imaging Center
- Other UI campus site - UI Fieldhouse, Department of Health & Human Physiology; Pappajohn Biomedical Discovery Building (PBDB)

VII.A.2 ***Is this project also being conducted by other researchers at their own sites (e.g. a multi-site collaborative project)?***
No

VII.B. Project Description (B)

VII.B.1. ***Does this project involve any of the following (Check all that apply):***

- [x] **Interventional** – Includes **Clinical (or Treatment) trial**, **Physiology intervention/study**, **Behavioral intervention/study**, **Diagnostic Trial**.
  - [x] **Clinical (or Treatment) trial** – A prospective biomedical or behavioral research study of new treatments, new drug or combinations of drugs, new devices, or new approaches to surgery or radiation therapy. (NIH and ClinicalTrials.gov & FDA)
  - [x] **Physiology intervention/study** – A pharmacologic or measurement study aimed at understanding basic mechanisms of disease and/or of normal human physiology, often without any therapeutic intent (though a clinical trial could include such components, often labeled as "translational" or "basic science" aims.) Measurements in such studies could include, but are not limited to, a blood draw, EKG, EEG, MRI, auditory or sensory testing, checking vital signs, DEXA scans, eye tracking, specimen collection, exercise, fasting, special diets, etc.
  - [ ] **Behavioral intervention/study** – May be used to refer to studies of individual or group behavior. This option does not include drugs, biologics, or devices but could include psychotherapy, lifestyle counseling, behavior modification, etc.
  - [ ] **Diagnostic trial** – Protocol designed to evaluate one or more interventions aimed at identifying a disease or health condition (ClinicalTrials.gov & FDA)
- [ ] **Observational**
- [ ] **Expanded Access** – A process regulated by the Food and Drug Administration (FDA) that allows manufacturers to provide investigational new drugs to patients with serious diseases or conditions who cannot participate in a clinical trial. Examples of expanded access include non-protocol access to experimental treatments, including protocol exception, single-patient IND, treatment IND, compassionate use, emergency use, continued access to investigational drug, and parallel track (ClinicalTrials.gov & FDA).
- [x] **Registry** – The collection and maintenance of data (not including biologic samples) in which: (1) the individuals in the registry have a common or related condition(s), and/or (2) the individuals in the registry are interested in being contacted for future studies by investigators other than those listed in Section II of this project.(UI Guide)
- [x] **Repository** – The collection, storage, and distribution of human biologic samples and/or data materials for research purposes. Repository activities involve three components: (i) the collection of data and/or specimens such as blood, tissue, saliva, etc.; (ii) the storage of data or specimens, and data management function; and (iii) the sharing of data/specimens with recipient investigators other than the original investigators. (paraphrased from OHRP)
- [ ] **Other**

VII.B.1.a ***Does this project involve any of the following (Check all that apply):***

- [ ] **Phase I trials** – include initial studies to determine the metabolism and pharmacologic actions of drugs in humans, the side effects associated with increasing doses, and to gain early evidence of effectiveness; may include healthy participants and/or patients (ClinicalTrials.gov & FDA)
- [x] **Phase II trials** – include controlled clinical studies conducted to evaluate the effectiveness of the drug for a particular indication or indications in patients with the disease or condition under study and to determine the common short-term side effects and risks(ClinicalTrials.gov & FDA)
- [ ] **Phase III trials** – include expanded controlled and uncontrolled trials after preliminary evidence suggesting effectiveness of the drug has been obtained, and are intended to gather additional information to evaluate the overall benefit-risk relationship of the drug and provide an adequate basis for physician labeling(ClinicalTrials.gov & FDA)
- [ ] **Phase IV trials** – studies of FDA-approved drugs to delineate additional information including the drug's risks, benefits, and optimal use(ClinicalTrials.gov & FDA)

VII.B.2 ***Does this project involve a drug washout (asking subject to stop taking any drugs s/he is currently taking)?***
No

VII.B.6 ***Will any subjects receive a placebo in this study when, if they were not participating, they could be receiving an FDA-approved treatment for their condition?***
No

VII.B.11 ***Is there a separate, written protocol that will be submitted in addition to this IRB New Project form? (Note: a grant application is not considered to be a protocol)***
No

VII.B.18 ***Does this project involve testing the safety and/or efficacy of a medical device?***
Yes

VII.B.19 ***Describe in detail procedures in place for maintaining device shipment and receipt records:***
N/A

VII.B.20 ***Who will be responsible for maintaining these shipment and receipt records?***
N/A

VII.B.21 ***Describe in detail procedures in place for tracking use and disposition of devices described in this study:***
N/A

VII.B.22 ***Who will be responsible for maintaining these use and disposition tracking records?***
The PI

VII.B.23 ***Describe in detail procedures in place to limit access to authorized study personnel for the storage, control, and dispensing of the investigational devices. (For example, investigational devices are kept in a locked area away from approved devices or have a keyed interlock, and only study personnel authorized to dispense the device have the keys)***
The device will be locked, key/card controlled room acessible only to the PI, Faculty Mentor, and laboratory staff.

VII.B.24 ***Is the device FDA-approved for the way it will be used in this study?***
No

VII.B.25 ***Is there an IDE (Investigational Device Exemption) for this device in this research project?***
No

VII.B.29 ***Indicate the appropriate FDA status you and/or the sponsor are requesting for the use of this device in this study.***
Non-Significant Risk (NSR) device/software

VII.B.31 ***Provide a detailed rationale for why this device meets the FDA definition of a Non-Significant Risk Device (NSR)***
Numerous studies used this device without any serious side effects. Additionally, the attachment "tDCS Safety" provides more details regarding the safety of tDCS.

VII.B.32 ***Provide a summary of prior investigations with this device.***
The PI and Dr. Rudroff (Faculty Mentor) used this device in previous studies, published in the journal Brain Sciences.

Furthermore, the IRB has approved protocols 201905826, 201905825, and 201906759 that are using this same device under similar stimulation parameters.

Workman, C.D., Fietsam, A.C., Rudroff, T. Transcranial Direct Current Stimulation at 4 mA Induces Greater Leg Muscle Fatigability in Women Compared to Men. Brain Sciences, doi: doi: 10.3390/brainsci10040244 (2020).

Workman, C.D., Fietsam A.C., Rudroff, T. Cerebellar Transcranial Direct Current Stimulation in People with Parkinson's Disease: A Pilot Study. Brain Sciences, doi: doi:

10.3390/brainsci10020096 (2020).

VII.B.33 ***Have there been any prior IRB reviews (at UI or elsewhere) and/or determinations made with regard to this device?***
Yes

VII.B.34 ***Provide a discussion of these reviews/determinations.***
The Faculty Mentor (Dr. Rudroff) used a tDCS device at Colorado State University. CSU IRB approved the protocols without any concerns. All protocols have been completed without any problems. Furthermore, our previous approved protocols (IRB #201905826, #201905825, #201906759, #202005124, #202002425, #201912430, and #202006616) included this same tDCS device.

VII.B.35 ***Has the FDA made an assessment of risk with regard to this device?***
Yes

VII.B.36 ***Has this device/software been approved by the FDA for another indication or in another form from its use in this project?***
No

VII.C. Project Description (C)

VII.C.1 ***Does this project involve any research on genes or genetic testing/research?***
No

VII.D. Project Description (D)

VII.D.1 ***Check all materials/methods that will be used in recruiting subjects (you will need to attach copies of all materials at the end of the application):***

- E-mail -
- Advertisements -
- Use of any information available to the researchers or their colleagues because this person is a patient OR use of any information considered to be Protected Health Information (PHI) OR review of patient/clinic records - The records reviewed in this project will be the clinical information contained in the patient's Epic file, generated as part of their clinical interaction with the providers in the MS clinic. Specifically we will evaluate their neurological examination, supporting evidence that they have MS, and their age.
- Other - Recruitment flyer

VII.D.2 ***List the individual data elements you will need to access/use from the patient or clinic records to identify potential subjects for recruitment***
Patient's name, age, medical record number, phone number, and email address
Data demonstrating that the patient has MS: history of neurological illness; MRI scan of brain and cervical spine; spinal fluid evaluation when available

VII.D.3 ***Describe why you could not practicably recruit subjects without access to and use of the information described above***
The patient’s in this study require the diagnosis of MS, which necessitates elaboration of their clinical history, MRI and spinal fluid data. In addition, the study requires asymmetry in the patient’s exam, which also requires access to the patient’s record, including the neurological exam.

VII.D.4 ***Describe why you could not practicably obtain authorization from potential subjects to review their patient or clinic records for recruitment purposes.***
Because of the requirement for the potential subjects to have MS, without access to records we would have no efficient way of determining potential subjects to approach.

VII.D.5 ***Describe plans to protect the identifiers from improper use or disclosure***
Patient data will be accessed only by authorized personnel, including Ms. Fietsam and Drs. Kamholz, Rudroff, Workman. Data derived from the studies outlined in this proposal will be de-identified and stored in a locked cabinet in Dr. Rudroff's laboratory. The key to the patient's identity will also be stored in the same place.

VII.D.6 ***Describe plans to destroy identifiers at the earliest opportunity consistent with conduct of the research***
The key to the patient identification will be kept in a locked cabinet in Dr. Rudroff's laboratory. The key will be destroyed once the studies are completed.

VII.D.7 ***Does the research team agree that the requested information will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the study, or for other research for which the use or disclosure of the requested information would be permitted by the HIPAA Privacy Rule***
Yes

VII.D.8 ***Will a member of the research team discuss the study with the subject in person prior to the subject agreeing to participate?***
Yes

VII.D.9 ***Describe the physical location where the consent process will take place:***
In the Integrative Neurophysiology Laboratory (INPL) (Department of Health & Human Physiology), N414 Field House or the MS Clinic.

VII.D.10 ***Will a member of the research team discuss the study with the subject by phone prior to the subject agreeing to participate?***
Yes

VII.D.11 ***Describe:***
The PI Ms. Fietsam, Dr. Rudroff, Dr. Kamholz, or Dr. Workman will explain and discuss the protocol before the subjects will be invited to the INPL.

VII.D.12 ***Who will be involved in the consent process (including review of consent document, answering subjects' questions)?***

Name	Consent Process Involvement
Alexandra Fietsam, MS	Yes
David Bushnell, MD	No
Justin Deters, MS	Yes
Lisa Dunnwald, MPH	No
Christine Gill, MD	Yes
Michael Graham, MD, PHD	No
John Kamholz, MD, PhD, MD	Yes
Shannon Lehman, BA	No
Parren McNeely, MD	No
Yusuf Menda, MD	No
Janet Pollard, MD	No
Laura Ponto, PHD	No
Thorsten Rudroff, PHD	Yes

VII.D.15 ***Check all materials that will be used to obtain/document informed consent:***
- Consent Document
- Verbal/Phone Script

VII.D.16 ***Are you requesting a waiver of documentation of consent (either no subject signature or no written document)?***
No

VII.D.19 ***Before the subject gives consent to participate are there any screening questions that you need to directly ask the***

potential subject to determine eligibility for the study?
Yes

VII.D.20 ***List any screening questions you will directly ask the potential subject to determine eligibility.***
See pre-consent questions in Attachments (Updated_ScreeningLog.docx)

VII.D.21 ***Will you keep a screening log or other record that would include information on people who do not enroll in the study?***
Yes

VII.D.22 ***Describe the information being collected and the purpose for keeping this information.***
The questionnaire and answers will be saved and stored in a safe location and may be used to contact the subjects for future studies.

VII.D.23 ***Will this information be shared with anyone outside the UI research team members?***
No

VII.D.25 ***After the subject agrees to participate (signs consent), are there any screening procedures, tests, or studies that need to be done to determine if the subject is eligible to continue participating?***
No

VII.D.27 ***Discuss how much time a potential subject will have to agree to consider participation and whether or not they will be able to discuss the study with family/friends before deciding on participation.***
There is no time limit.

VII.D.28 ***How long after the subject agrees to participate do study procedures begin?***
As soon as possible.

VII.D.29 ***Provide a description of the enrollment and consent process for adult subjects***

- ***Describe each study population separately including control population***
- ***Include when recruitment and consent materials are used***
- ***Use 3rd person active voice "The Principal Investigator will identify subjects. For example, the principal investigator will identify potential subjects, the study coordinator will discuss the study with subjects over the telephone and schedule the first study visit, etc..."***
- ***Describe the steps that will be taken by the research team to minimize the possibility of coercion or undue influence during the consent process***

Prospective participants, men and women with MS, will be recruited from the MS Clinic in the Dept. of Neurology at UIOWA (Dr. John Kamholz), through mass email, and through advertisements on UIOWA Campus. For those recruited at the clinic, Dr. Kamholz will discuss the study with potential participants and provide them with a copy of the informed consent and/or consent summary (if requested) and a copy of the recruitment flyer to contact the other study personnel. All other experimental procedures will be performed in the INPL (Director: Thorsten Rudroff, PhD, FACSM). Interested individuals from any recruitment source (i.e., clinic, flyers, website) will contact study personnel and perform an initial phone screening via a questionnaire. Contact information for the prospective participant will be accessible only to the research staff according to HIPPA regulations. After completion of the phone questionnaire, INPL personnel will schedule the participant's first visit (14 total), during which they will review the consent summary and consent form before signing the consent document. During the potential subject's first visit, the PI or research staff will answer all questions asked by the potential subject and the subject will be informed of all potential risks before the signing the consent document. Subjects will in no way be coerced to sign the consent form and will be informed that it is their choice whether to volunteer for this study. Even after subjects sign the consent, they are free to withdraw from the study at any time and for any reason. In the screening form and consent document, we ask participants to indicate if they would like to placed into our registry so they could be contacted for future studies by our lab and by other researchers not involved in this particular study. If they allow, we will keep their information secure on a password-protected computer in a restricted access office. If requested, their information will be permanently removed from our contact list.

VII.D.37 ***Does the study include any form of deception (e.g., providing participants with false information, misleading information, or withholding information about certain study procedures)?***

Examples:

- ***Procedure includes a cover story that provides a plausible but inaccurate account of the purposes of the research.***
- ***Participants will be provided with false information regarding the particular behaviors of interest in the research.***
- ***Procedures include a confederate pretending to be another participant in the study.***
- ***Participants will be told that the research includes completion of a particular task, when in fact, that task will not be administered.***
- ***Study is designed to introduce a new procedure (or task) that participants are not initially told about.***
- ***If yes, a waiver of informed consent must be requested under question IV.3.***

No

VII.E. Project Description (E)

VII.E.1 ***Will subjects be randomized?***
Yes

VII.E.1.a ***Will any subjects be blinded to which study arm they have been assigned?***
Yes

VII.E.1.b ***Does the protocol permit telling subjects their treatment assignment at the end of the entire study?***
Yes

VII.E.1.c ***Describe the circumstances under which subjects will be told what study arm they have been assigned.***
At the end of all sessions the participant will be informed about the study arm in which they were
involved.

VII.E.2 ***Describe randomization scheme/assignment including ratio such as 1:1, 2:1 etc.***
The study will be a double-blind and sham-controlled. Forty participants will be randomly assigned into four groups (Sham and balance training, 4 mA tDCS and balance training, sham and gait training, and 4 mA and gait training). Participants will undergo 9 sessions of tDCS combined with either gait or balance training.

VII.E.3 ***Will any questionnaires, surveys, or written assessments be used to obtain data directly from subjects in this study?***
Yes

VII.E.4 ***List all questionnaires, surveys, written assessments and ATTACH each one to the application. (NOTE: You are NOT prohibited from attaching copyrighted materials to this application)***
Patient Determined Disease Steps (PDDS)
Fatigue Severity Scale (FSS)

VII.E.5 ***Does this project involve creating any audiotapes, videotapes, or photographs?***
No

VII.E.6 ***Provide a detailed description in sequential order of the study procedures following the consent process - DO NOT cut and paste from the Consent Document.***

Describe study populations separately if they will be participating in different procedures - include CONTROL population if applicable.

DESCRIBE:

- ***What subjects will be asked to do/what happens in the study (in sequential order)***
- ***The time period over which procedures will occur***
- ***The time commitment for the subject for individual visits/procedures***

- ***Long-term followup and how it occurs***

PwMS will be randomly assigned to one of four groups: ctDCS and gait training, sham and gait training, ctDCS and balance training, or sham and balance training (n = 12 per group). Each subject will attend a total of 14 experimental sessions. Session 1 will be a familiarization session and will last approximately 45 minutes. The duration of the baseline (Session 2) and 24-hour post-intervention session (Session 12) will be approximately 3 hours. The ctDCS and gait training sessions (Sessions 3 – 11) will last approximately 1.5 hours. Finally, the two- and four-week post-intervention sessions (Sessions 13 and 14, respectively) will be approximately one hour. During the initial session, subjects will be consented and complete strength testing to objectively determine the more-affected leg. Additionally, during Session 1 subjects will become familiar with treadmill walking and determine a self-selected speed for subsequent testing sessions. During the baseline session (Session 2), subjects will 1) complete the Fatigue Severity Scale (FSS)63, 2) undergo a whole-body FDG/PET scan after 20 minutes of treadmill walking at their self-selected speed, 3) perform the Functional Gait Assessment (FGA), 4) Timed 25-Foot Walk Test (T25WT), 5) Berg Balance Scale (BBS), 6) static posturography, and 7) the 6-minute walk test (6MWT) while wearing inertial sensors. The following 9 days will include 20 minutes of either 4 mA or sham ctDCS, 10 minutes of rest to allow for peak stimulation effects, and then approximately 40 minutes of gait or balance training. Session 12 will consist of the same testing battery as Session 2. Long term effects (2- and 4-weeks post-intervention) will be assessed with the 1) FSS questionnaire, 2) FGA, 3) T25FW, 4) BBS, 5) static posturography, and 6) the 6MWT during Sessions 13 and 14.

STRENGTH TESTING: Strength testing will be performed in a sitting position on an isokinetic dynamometer (CSMi, Stoughton, MA, USA). The subject will be secured with Velcro bands to help isolate the knee joint and the range of motion will be set between 100° and 0° of flexion. Strength testing will begin with a 15-repetition warm up of the knee extensors and flexors at 60º/s (concentric/concentric). After a 30 second rest, 3 sets of 1 maximal effort isometric contraction of the knee extensors and flexors will be performed at 65° and 30°, respectively, with ≥ 30 s of rest between each set. Isokinetic strength testing will consist of 3 sets of 1 maximal effort knee extension and flexion (60°/s, concentric/concentric) with ≥ 30 s of rest between each set. All testing will be completed on both legs and the largest torque obtained from a given muscle group in any of the strength testing conditions (isometric or isokinetic) will be used to verify leg dominance.

FUNCTIONAL GAIT ASSESSMENT (FGA): The FGA is a valid measure of walking balance and consists of 10 challenging tasks, such as walking with a narrow base of support (i.e., tandem stance), walking backwards, and walking with eyes closed. Each item is graded from 0 (severe impairment) to 3 (normal performance), with a maximum score of 3068. The minimal clinical important difference (MCID) for the FGA has not been established in PwMS. However, in other neurological populations, a MCID of 4-6 points has been suggested.

TIMED 25-FOOT WALK TEST (T25FW): The T25FW test resembles relevant daily life situations, such as walking across a signaled intersection, is well-established and has very good psychometric properties. In a cordoned-off hallway, subjects will be instructed to walk as fast as possible between two points separated by 25 feet during two separate trials65. The shortest time it takes to complete the 25-foot walk will be the main outcome variable. Gait characteristics will also be recorded using six inertial sensors (OPAL inertial motion units [APDM, Portland, OR, USA]) located on the chest/sternum, each wrist and foot, and on the lower back (5th lumbar). A 20% decrease in the time it takes to complete the T25FW has been established as a significant change in PwMS.

BERG BALANCE SCALE (BBS): The BBS is a valid and reliable assessment of balance during static (e.g., standing with eyes closed) and dynamic (e.g., completing a 360-degree turn) conditions. A cut-off score of 44 has been established as a criterion to identify PwMS with a high fall risk. Furthermore, it has been shown that the minimal clinically important difference (MCID) for the BBS in PwMS is 3 points.

STATIC POSTUROGRAPHY: Static posturography will be examined on a Balance Plate (Balance Tracking Systems, San Diego, CA, USA). Participants will stand on both firm (i.e., the force plate) and compliant (i.e., a 6 cm Airex Balance Pad Elite 76 [Airex AG, Sins, Switzerland] placed on the force plate) surfaces with their eyes open and with their eyes closed for one minute each. The addition of a foam pad increases the difficulty of maintaining balance by changing foot pressure distribution and decreases the input of cutaneous mechanoreceptors and joint receptors. The center of pressure average movement velocity in the anterior-posterior and medial-lateral directions and the area of an ellipse that encapsulates 95% of the 2D area explored will be the primary outcomes.

6-MINUTE WALK TEST (6MWT): The 6MWT is considered the “gold standard” for a long walking test in interventional research. The subjects will be led to a cordoned-off hallway to perform the walk. Subjects will be instructed to walk as far as possible between two points separated by 30 m for 6 min. Gait characteristics and distance walked will be calculated and recorded using six inertial sensors (OPAL inertial motion units [APDM, Portland, OR, USA]) located on the chest/sternum, each wrist and foot, and on the lower back (5th lumbar).

GAIT TRAINING: The gait training protocol is aimed to improve walking velocity, balance, fatigability, and cognitive functions during motor dual tasks. This protocol has been used previously by Jonsdottir et al. (2018, 2020) and resulted in significant improvements in fatigability, speed, and mobility with a moderate improvement in balance measures. The treadmill training will be performed without body weight support, but subjects may hold onto handrails for balance support if necessary. The exercise intensity will be based on the participant's Rate of Perceived Exertion (RPE) on a scale from 0-10 and the training goal will be to maintain an intensity between 5-6. Therefore, treadmill speed and slope will be regulated based on relative intensity. Heart rate will also be monitored with a heart rate strap placed around the chest. The treadmill training sessions will consist of three different walking bouts: 1) Aerobic bout (minutes 0-12): preferred walking speed for the first 3 minutes, then the treadmill speed and slope will be increased as necessary to maintain the desired RPE range until the end of minute 12. RPE will be maintained between 5-6 and heart rate will not exceed 80% of age-predicted maximum heart rate. 2) Dual-task phase (minutes 13-22): preferred walking speed will be maintained while the participant completes motor dual-task activities such as changing walking motions (e.g., long steps, walking on toes, and knee lifts), head rotations, and walking with eyes closed. 3) Second aerobic phase (minutes 23-34): increase in walking speed and slope as necessary to maintain the desired RPE until the end of minute 31. RPE will be kept between 5-6 and heart rate will remain below 80% of age-predicted maximum heart rate. The last three minutes will consist of walking at their preferred speed.

BALANCE TRAINING: The balance training protocol will be based on previous work by Hebert et al. (2011) and will include a variety of both static and dynamic balance exercises on both compliant (i.e., foam and trampoline) and firm surfaces46. Example exercises include performing head rotations and ball catching and tossing during walking and while using a variety of increasingly difficult stances (i.e., heels and toes together, half-tandem, and full tandem stance). Each training session will last approximately 40 minutes.

tDCS PROTOCOL: A tDCS device (Soterix) will deliver a small direct current through two sponge surface electrodes (5 cm × 7 cm) soaked with ~15 mL of NaCl saline. The middle of the medial edge of the positive electrode (anode) will be positioned 1 cm below and 2 cm lateral to the inion over the cerebellar hemisphere ipsilateral to the more MS-affected side. The negative electrode (cathode) will be placed with the medial edge 1 cm below and 2 cm lateral to the inion over the cerebellar hemisphere contralateral to the more MS-affected side (bilateral montage). Stimulation will be administered for 20 minutes with the subject seated comfortably in a chair. Active stimulation will start with a 30 s ramp-up to the target intensity (4 mA), after which the intensity will be maintained for 20 min before being ramped-down to 0 mA over 30 s.

SHAM PROTOCOL: During sham, the tDCS device automatically administers a 30 s ramp-up immediately followed by a 30 s ramp-down both at the beginning and the end of the 20 min stimulation period; in the intervening time, the intensity will be maintained at 0 mA.

WHOLE BODY IMAGING: Prior to FDG administration, subjects will be asked to fast for a minimum of 6 hours. Blood glucose will be checked and must be ≤ 200 mg/dL to proceed with the imaging. FDG (5 mCi ± 10% IV) will be administered two minutes into the twenty-minute treadmill walking task during Sessions 2 and 12. CT imaging will be performed with emission imaging for attenuation correction and anatomical localization.

VII.E.7 ***Will you attempt to recontact subjects who are lost to follow-up?***
No - those lost to followup will not be recontacted

VII.E.9 ***Will subjects be provided any compensation for participating in this study?***
Yes

VII.E.10 ***Cash***
No

VII.E.11 ***Gift Card***
No

VII.E.12 ***Check***
Yes

VII.E.13 ***Who will be providing the research compensation check to the subject?***
Accounting Services directly via the e-Voucher system

VII.E.16 ***Other***

No

VII.E.19 ***Describe the compensation plan including***

- ***Compensation amount and type per visit***
- ***Total compensation***
- ***Pro-rating for early withdrawal from study***

Subjects will be compensated $150 ($80 for 9 intervention [tDCS and training] session and $70 for imaging sessions) for their time, effort, and parking costs upon completion of the study. Subjects will receive payment within two weeks of the completion of their last session (including withdraws).

VIII. Risks

VIII.1 ***What are the risks to subjects including***
- emotional or psychological
- financial
- legal or social
- physical?

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 a temporary headache, skin redness under the electrodes, and/or tingling, itching, and burning sensations 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/cm^2, whereas the current densities used in human studies are between 0.04 and 0.08 mA/cm^2 and in this proposal are 0.06 mA/cm^2 and 0.011 mA/cm^2. 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 probability is very unlikely that harm may occur (see above). Based on the available 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 of performing motor tasks: There is potential for injury (muscle strain) resulting from the walking and balance tests and training. There is also a potential for falling during the balance tasks, particularly for PwMS, who have a higher fall risk in general. Other risks may include feelings of anxiety and/or stress induced by the experiment, which can lead to an increase in heart rate and blood pressure.

PET Imaging: This study involves the administration of a PET radiopharmaceutical, [18F]fluorodeoxyglucose (FDG). FDG has been used at the University of Iowa and throughout the world for a variety of conditions. There have been a few reports of relatively rare side-effects involving temporary low blood pressure and allergic reactions. As a result of participating in this research, each subject will receive a dose of radiation equivalent to approximately 90% of the dose that a medical radiation worker can accrue yearly. Although there are no proven harmful effects from the level of radiation exposure in this study, long-term effects on a subject's health cannot be ruled out with certainty. Pregnancy is a contraindication to PET imaging. Thus, all women of childbearing potential will undergo a pregnancy test before PET imaging. Injection of tracers will require the placement of an intravenous catheter. As in any procedures involving catheters placed in veins, there are several risks, including infection, clotting, or continued bleeding. There may also be bruising, skin irritation, and a dull ache at the site of injection. The subject will be asked to fast for a minimum of 6 hours

prior to the FDG study. There is a small risk of hypoglycemia associated with this fast.

Risks of MRI: Participants may be uncomfortable inside the MRI scanner if they do not like to be in closed spaces ("claustrophobia"). During the procedure, they will be able to talk with the MRI staff through a speaker system. Participants can stop the scan at any time.

The MRI scanner produces a loud hammering noise, which has produced hearing loss in a very small number of patients. Participants will be given noise-canceling headphones to reduce this risk. A metal object flying through the air toward the magnet and hitting the participants presents the greatest risk associated with MRI. To reduce this risk, we require that all people involved with the study remove all metal from their clothing and pockets. No metal objects will be brought into the magnet room while participants are inside the room. In addition, the door to the room will remain closed throughout the study so that no one can accidentally bring a metal object into the room.

There are no known risks associated with limited exposure to magnetic fields. Magnets of this strength have been in use for medical imaging for over 15 years. However, we will keep a record of the length of time participants were in the magnet, as well as the amount of radio waves used during that time.

Although the risk is minimal, there is a risk for breach of confidentiality.

VIII.2 ***What have you done to minimize the risks?***

- ***If applicable to this study ALSO include:***
  - ***How you (members of your research team at Iowa) will monitor the safety of individual subjects.***
  - ***Include a description of the availability of medical or psychological resources that subjects might require as a consequence of participating in this research and how referral will occur if necessary (e.g. availability of emergency medical care, psychological counseling, etc.)***

All risks will be minimized by using safe, well-established procedures and strict monitoring of each experimental session. Study staff will be in close proximity to each subject to help prevent/minimize fall risk and muscle strain. Furthermore, risk will be 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).

The venous catheter will be inserted by an individual from the PET Center that is qualified, trained, and experienced at inserting venous lines.

Because the subject will be asked to fast for a minimum of 6 hours, there is a small risk of hypoglycemia. Prior to the injection of FDG, the blood glucose level will be checked. If the subject is found to be hypoglycemic at that time, glucose will be administered orally (e.g., juice) or by IV depending on the subject's level and symptoms.

VIII.3 ***Does this study have a plan to have an individual or committee review combined data from all subjects on a periodic basis (such as summary or aggregate safety and/or efficacy data)?***
No

IX. Benefits

IX.1 ***What are the direct benefits to the subject (do not include compensation or hypothesized results)?***
There is no personal benefit associated with this protocol.

IX.2 ***What are the potential benefits to society in terms of knowledge to be gained as a result of this project?***
The outcomes may help to improve rehabilitative procedures for people with MS who have gait or balance impairments.

X. Privacy & Confidentiality

X.1 ***What are you doing to protect the privacy interests of the subjects?***
Subjects will be consented in a private room (i.e., room N414 of the Field House)or during a phone call at a time where the subject is comfortable discussing screening questions. During data collection, we will only collect the minimum amount of information necessary to answer the research question.

X.2 ***Are you collecting the Social Security Number of any subjects for any purpose?***
Yes

X.3 ***Provide the intended usage of SSN:***
- To provide compensation to subjects

X.4 ***How will information/data be collected and stored for this study (check all that apply):***
- Electronic records (computer files, electronic databases, etc.) - All data collected, including personal identifiable information, will be stored electronically on University of Iowa secured networks, with access restricted to the current investigators.
  - Name - Bryan Ringen
  - Title - IT Support Consultant
  - University Job Classification - Faculty/Staff
- Paper/hard copy records (hard copy surveys, questionnaires, case report forms, pictures, etc.) - Hard copy data will be stored in a locked file cabinet accessible only by research personnel. At night, the second story of the Health and Human Physiology Department is restricted to authorized key holders, and the room in which the file cabinet is located is restricted to only current laboratory staff.

X.5 ***Do the confidentiality protections indicated above allow only members of the research team to access the data/specimens?***
Yes

X.7 ***Does your study meet the NIH criteria for a Certificate of Confidentiality or will you be applying for Certificate of Confidentiality?***
No

XI. Data Analysis

XI.1 ***Describe the analysis methods you will use, including, if applicable, the variables you will analyze***
All imaging data will be transferred to the Integrative Neurophysiology Lab in the Department of Health and Human Physiology for analysis. The prior and post-treatment FDG images will be co-registered to the anatomical CT images. Anatomically based volumes-of-interest (VOIs) will be generated manually using the View tool of PMOD. In the upper leg, the knee extensors (rectus femoris, vastus medialis, vastus intermedius, and vastus lateralis) and knee flexors (long and short head of the biceps femoris, semimembranosus, semitendinosus, sartorius, and gracilis) will be identified. In the lower leg, the plantar flexors (gastrocnemius, soleus, peroneus longus, peroneus brevis, flexor digitorum longus, flexor hallucis longus, and tibialis posterior) and the dorsiflexors (tibialis anterior, extensor digitorum longus, and extensor hallucis longus) will be identified. Standardized uptake values (SUV) based on the injected dose and body weight will be calculated for each muscle. Although the participants will fast for a minimum of 6 hours to minimize the impact of endogenous glucose and insulin, SUVs may be affected by blood glucose and insulin levels. Therefore, the SUV data will be analyzed without normalization and, separately, as values normalized to standard blood glucose (adjusted to 100 mg/dL) and/or by using the liver as a reference tissue to allow for comparison across experimental sessions. The data will be analyzed using PMOD Version 4.001 (PMD Technologies LLC, Zürich, Switzerland). Asymmetry indices (AIs) will be calculated to determine the magnitude of asymmetry in SUVs between the legs using a previously used equation23,82. An AI greater than 10% will be considered asymmetric. Spearman's correlation will be used to test whether the change in FDG uptake is significantly related to the change in walking and balance scores after ctDCS and training. We will use a liberal significance threshold to avoid type II errors because the relatively low number of subjects in this study leads to conservative testing. The level of statistical significance for all brain imaging analyses is $p < 0.005$ without correction.

A stimulation (sham vs. 4 mA) by training (balance vs. gait) by time (24 hours, 2 weeks, and 4 weeks) ANCOVA with baseline measurements as covariates will be conducted on each outcome variable (e.g., distance walked on the 6MWT and FGA score) to compare the short- and long-term effects of gait and balance training combined with ctDCS. Levene's test and normality tests (QQ plots, Shapiro Wilk test, and histograms) will be used to test the statistical assumptions. Post-hoc testing (paired and unpaired t-tests) and effect sizes (Cohen's d) will be calculated to clarify significant main or interaction effects. Significance will be accepted at p ≤ 0.05 and adjusted with a Bonferroni correction. Statistical analyses will be performed using SPSS 27 (IBM Corp, Armonk, NY, USA).

XI.2 ***Provide the rationale or power analysis to support the number of subjects proposed to complete this study.***

We used effect sizes (Cohen's d = 2.08 and 1.37, respectively) from Pilloni et al. 202060 and Hebert et al. 201146 to calculate the required sample size. With a significance fixed at p = 0.05 and 80% power, we will require 40 total subjects (n = 10 in each group) to properly power the hypothesis test for a statistically significant change. Based on this calculation and the assumption of a standard drop out rate of approximately 20%, we propose to recruit 48 total subjects (n = 12 in each group).

XII. Future Research

XII.1 ***Do you wish to keep any information about subjects involved with this research project so that members of the current research team may contact them in the future for your own research projects?***
Yes

XII.2 ***Do you wish to keep any information about subjects involved with this research project so that other researchers may contact them for future research?***
Yes

XII.3 ***List the data or information you will keep:***
Contact information and outcome of the phone questionnaire.

XII.4 ***Does this project involve storing any data, tissues or specimens for future research?***
Yes – contribution for future use is mandatory for participation in the study