Study Protocol June 20, 2022 IRB aproved 02/14/19

NCT03757819 Transcranial Direct Current Stimulation and Walking in Multiple Sclerosis

A single-blind, sham-controlled, randomized, cross-over design was employed. Subjects attended three experimental sessions. In the first session, participants gave consent, completed the isokinetic strength testing of the knee extensors and flexors to objectively determine the more-affected leg, and self-selected a comfortable walking speed on the treadmill to be used during sessions 2 and 3. At least three days after the first session, Session 2 was completed. Sessions 2 and 3 were separated by at least seven days to allow tDCS effects to dissipate. Prior to sessions 2 and 3, the participants were asked to fast for a minimum of 6 h before FDG administration. At the beginning of sessions 2 and 3, the participants' height and weight were measured, blood glucose levels were determined, and an IV catheter was inserted for FDG injection. Blood glucose level was required to be equal to or less than 200 mg/dL in order to proceed with FDG administration and PET scanning. During sessions 2 and 3, either Sham (0 mA) or tDCS (3 mA) was applied (determined through randomization) to the motor cortex (M1) area corresponding to the more-affected leg for 20 min. The purpose (e.g., enhancing motor learning or improving motor performance) of tDCS may determine stimulation timing. Studies on motor learning often apply tDCS during a task to improve acquisition. In contrast, tDCS was applied before the motor performance of a well-learned task (walking) in the current study. It has previously been demonstrated that tDCS has ambiguous effects on cortical excitability during stimulation, but significantly and consistently increased cortical excitability after stimulation [48]. Moreover, when comparing tDCS before and during a 6-min walk test in PwMS, it was found that stimulation before increased gait velocity, whereas stimulation during resulted in a decrease in the distance walked. Therefore, in this study participants underwent 20 min of tDCS then rested for 10 min to allow for peak stimulation effects before walking on a treadmill for 20 min. Ratings of Perceived Exhaustion (RPE) were collected at the end of each minute during the walking task. Approximately two minutes into treadmill walking, 10 ± 10% mCi of FDG was administered via IV injection. Immediately after walking was completed, participants were positioned in the PET/computed tomography (CT) scanner and a whole body (top of head to toes) scan was completed to evaluate glucose uptake in the leg muscles.

Data Analysis

Twenty regions of interest (ROIs) were drawn on the CT scan from each experimental session to locate the skeletal muscles of the lower limbs. 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) were 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) were identified. The PET images were acquired immediately after the treadmill task and, therefore, the glucose uptake values closely reflected the uptake of FDG during walking. Standardized uptake values (SUV) based on the injected dose and body weight were calculated for each muscle. Although the participants fasted for a minimum of 6 h in order to minimize the impact, SUVs may be affected by blood glucose and insulin levels. Therefore, the SUV data were analyzed without normalization and as values normalized to standard blood glucose (adjusted to 100 mg/dL), and/or the liver as a reference tissue, to allow for comparison across experimental sessions. The data were analyzed using PMOD Version 4.001 (PMD Technologies LLC, Zürich,

Switzerland). The more-affected (weaker) legs were assigned using the knee extensor torque data obtained in Session 1. Asymmetry indices (AIs) were calculated to determine the magnitude of the asymmetry in SUVs between the legs using a previously used equation (Equation (1)). An AI greater than 10% was considered asymmetric.

Statistical Analysis

In order to compare muscle activity between the legs and experimental sessions, SUVs were averaged for each muscle group (knee extensors, knee flexors, plantar flexors, and dorsiflexors). The assumptions for normality were investigated via histograms, Q-Q plots, and the Shapiro-Wilk test, but were not met. Therefore, nonparametric paired tests (Wilcoxon tests) were performed on the normalized data to compare the muscle groups of the left and right leg within each condition (e.g., left vs. right knee extensors during the tDCS condition) and to compare the muscle groups of each leg between conditions (e.g., left knee extensors in Sham vs. tDCS). Significance was accepted at $p < 0.05$. Analyses were performed using GraphPad Prism 8.1.2 (GraphPad Software, San Diego, CA, USA).

INFORMED CONSENT DOCUMENT

Project Title: **Can Transcranial Direct Stimulation Improve Walking in Multiple Sclerosis?**

Principal Investigator: Thorsten Rudroff, PhD

Research Team Contact: Thorsten Rudroff, PhD (319) 467-0363
John Kamholz, MD, PhD

This consent form describes the research study to help you decide if you want to participate. This form provides important information about what you will be asked to do during the study, about the risks and benefits of the study, and about your rights as a research subject.

- If you have any questions about or do not understand something in this form, you should ask the research team for more information.
- You should discuss your participation with anyone you choose such as family or friends.
- Do not agree to participate in this study unless the research team has answered your questions and you decide that you want to be part of this study.

WHAT IS THE PURPOSE OF THIS STUDY?

This is a research study. We are inviting you to participate in this research study because you are between 18 and 70 years of age, and you were diagnosed with Multiple Sclerosis (MS).

The purpose of this research study is to determine if a single session of transcranial direct current stimulation (tDCS) can improve walking in people with MS. A second purpose is to find out whether tDCS should be applied before or during walking.

tDCS is a non-invasive technique in which a very weak electrical current is applied to the head in order to stimulate the brain.

HOW MANY PEOPLE WILL PARTICIPATE?

Approximately 40 people will take part in this study conducted by investigators at the University of Iowa.

HOW LONG WILL I BE IN THIS STUDY?

If you agree to take part in this study, you will be asked to participate in three sessions on three different days separated by no less than 5 days. Each visit will last approximately 60 minutes.

WHAT WILL HAPPEN DURING THIS STUDY?

Upon arrival to the Integrative Neurophysiology Laboratory (NIPL) on the IOWA Campus the investigators will explain the protocol procedures. You will be assigned to one of two groups. If you agree to participate in the study and sign the consent document, you will complete the Patient Determined Disease Steps Scale (PDDS), the Fatigue Severity Scale (FSS), and a 6 Minute Walk Test (MWT) for baseline performance. Your maximal strength of your right and left leg muscles will be performed to determine your more-affected leg**.** You will sit on a chair and you will be asked to extend your knee against a pad as strong as possible.

If you are in group 1, the second session will involve a 6 MWT in which you receive tDCS or Sham (no electrical current) before the 6 MWT. In the third session you will receive the application (tDCS or Sham) which was not used in the first session. If you are in group 2, the second session will involve a 6 MWT in which you receive tDCS or Sham during the 6 MWT. In the third session you will receive the application which was not used in the first session. We will also measure gait speed, cadence, stride length and time, step length and time during the walk test.

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.

WHAT ARE THE RISKS OF THIS STUDY?

You may experience one or more of the risks indicated below from being in this study. In addition to these, there may be other unknown risks, or risks that we did not anticipate, associated with being in this study.

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. We will follow the current guidelines for safe and effective stimulation that have been identified for research studies and in clinical practice for tDCS applications. 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.

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 Performing Motor Tasks

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.

You can stop the contractions immediately if you 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 risks 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.

General Risk

Even though the risk is minimal, there is a risk for breach of confidentiality. We will protect your information using the methods describes later in this document, in the section, "What About Confidentiality?"

WHAT ARE THE BENEFITS OF 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.

WILL IT COST ME ANYTHING TO BE IN THIS STUDY?

You will not have *any* costs for being in this research study. All procedures and tests will be provided at no cost to you. You/your health insurance company will remain responsible for your regular medical care expenses that are not part of this study.

WILL I BE PAID FOR PARTICIPATING?

You will be paid for being in this research study. You may need to provide your address if a check will be mailed to you.. Once you have completed the study you will receive $100.

WHO IS FUNDING THIS STUDY?

The National Multiple Sclerosis Society is funding this research study. This means that the University of Iowa is receiving payments from **MS Society** to support the activities that are required to conduct the study. No one on the research team will receive a direct payment or increase in salary from **the MS Society** for conducting this study.

WHAT ABOUT CONFIDENTIALITY?

We will keep your participation in this research study confidential to the extent permitted by law. However, it is possible that other people such as those indicated below may become aware of your participation in this study and may inspect and copy records pertaining to this research. Some of these records could contain information that personally identifies you.

- federal government regulatory agencies,
- The food and Drug Administration
- auditing departments of the University of Iowa, and
- the University of Iowa Institutional Review Board (a committee that reviews and approves research studies)

To help protect your confidentiality, we will keep private all research records that identify you Your data will be coded to remove any direct links to your identity, and any identifying material will be locked in a secure filing cabinet. . If we write a report or article about this study or share the study data set with others, we will do so in such a way that you cannot be directly identified.

The University of Iowa Hospitals and Clinics generally requires that we document your participation in research occurring in a University of Iowa Health Care facility. This documentation will be in either your medical record or a database maintained on behalf of the institution reflecting that you are participating in this study. The information included will provide contact information for the research team as well as information about the risks associated with this study. We will keep this Informed Consent Document in our research files; it will not be placed in your medical record chart.

A description of this clinical trial will be available on http://www.ClinicalTrials.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 any time.

IS BEING IN THIS STUDY VOLUNTARY?

Taking part in this research study is completely voluntary. You may choose not to take part at all. If you decide to be in this study, you may stop participating at any time. If you decide not to be in this study, or if you stop participating at any time, you won't be penalized or lose any benefits for which you otherwise qualify.

What if I Decide to Drop Out of 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.

Will I Receive New Information About the Study while Participating?

If we obtain any new information during this study that might affect your willingness to continue participating in the study, we'll promptly provide you with that information.

WHAT IF I HAVE QUESTIONS?

We encourage you to ask questions. If you have any questions about the research study itself, please contact: Thorsten Rudroff, (319) 467-0363**.** If you experience a research-related injury, please contact: Thorsten Rudroff, (319) 467-0363.

If you have questions, concerns, or complaints about your rights as a research subject or about research related injury, please contact the Human Subjects Office, 105 Hardin Library for the Health Sciences, 600 Newton Rd, The University of Iowa, Iowa City, IA 52242-1098, (319) 335-6564, or e-mail irb@uiowa.edu. General information about being a research subject can be found by clicking "Info for Public" on the Human Subjects Office web site, http://hso.research.uiowa.edu/. To offer input about your experiences as a research subject or to speak to someone other than the research staff, call the Human Subjects Office at the number above.

This Informed Consent Document is not a contract. It is a written explanation of what will happen during the study if you decide to participate. You are not waiving any legal rights by signing this Informed Consent Document. Your signature indicates that this research study has been explained to you, that your questions have been answered, and that you agree to take part in this study. You will receive a copy of this form.

Subject's Name (printed): _____

Do not sign this form if today's date is on or after EXPIRATION DATE: 11/08/19.

_____ _____

(Signature of Subject) (Date)

Statement of Person Who Obtained Consent

I have discussed the above points with the subject or, where appropriate, with the subject's legally authorized representative. It is my opinion that the subject understands the risks, benefits, and procedures involved with participation in this research study.

_____ _____

(Signature of Person who Obtained Consent) (Date)