Project Title: Transcranial Direct Current Stimulation (tDCS) for Post COVID-19 Fatigue

NCT 04876417

April 13, 2023

tDCS for COVID-19 fatigue

PI: Thorsten Rudroff
IRB ID #: 202009381

Project Details

I. Project Introduction

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

I.2 ***Project Title:***
Transcranial direct current stimulation (tDCS) for the treatment of fatigue in post-COVID-19 patients

I.3 ***Short Title (optional):***
tDCS for COVID-19 fatigue

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.***

For survivors of severe COVID-19, overcoming the virus is just the beginning of an uncharted recovery path. As the number of confirmed COVID-19 cases exceeds 27 million globally and 6 million in the US, the number of patients who experience persistent symptoms during recovery is rapidly growing. In COVID-19 patients, common acute symptoms include cough, fever, dyspnea, musculoskeletal symptoms (myalgia, joint pain, fatigue), gastrointestinal symptoms, and anosmia/dysgeusia [1,2]. Clinicians and researchers have focused on the acute phase of COVID-19, but continued monitoring and treating of persistent symptoms is urgently needed. Recent studies [3, 4] assessed persistent symptoms in patients who were discharged from the hospital after recovering from COVID-19. None of the patients had a fever or any of the other signs or symptoms associated with acute illness. Nevertheless, decreased quality of life was observed in 44.1% and fatigue was reported by 53.1% [3] and 71% [4] of patients. Furthermore, persistent fatigue following COVID-19 infection is common and independent of severity of initial infection (hospitalized and non-hospitalized patients) [5]. In addition to the characteristic laboratory findings and lung computed tomography (CT) abnormalities [6], it has been recently reported that patients with COVID-19 also have neurological manifestations [7-9]. Wu et al. [8] found that viral infections have detrimental impacts on neurological functions and can even cause severe neurological damage. Their study showed that coronaviruses (CoV), especially severe acute respiratory syndrome CoV 2 (SARS-CoV-2), exhibited neurotropic properties and may cause neurological diseases with severe fatigue symptoms. Another recent case report has also indicated reduced glucose uptake ([18F]flurodeoxyglucose (FDG); measured with positron emission tomography (PET)) in diverse brain areas [9], which may contribute to these neurological manifestations. Therefore, there is a critical need to develop inexpensive, effective, and rapid treatments for the persistent fatigue experienced by recovered COVID-19 patients. Without such treatments, these patients will continue to experience fatiguing symptoms that significantly reduce their quality of life. One possible treatment modality is transcranial direct current stimulation (tDCS) [10]. tDCS uses weak currents applied to the scalp to alter the excitability of cortical neurons by changing their spontaneous firing rate. It also has a favorable safety profile and only transient adverse side effects. Studies in patients with neurological disorders have shown that tDCS over the primary motor and/or sensory cortex (M1/S1) consistently and significantly improves fatigue [11-13]. M1 tDCS represents an easy, cost-effective candidate for treating persistent fatigue in recovered COVID-19 patients.

I.5 ***Specify your research question(s), study aims or hypotheses (do not indicate "see protocol")***

The objective of this application is to investigate the short- and long-term effects of multiple sessions of 4 mA M1 tDCS on fatigue and brain activity in recovered COVID-19 patients using established measures of perception of fatigue, performance fatigability, and cerebral glucose uptake. Our central hypothesis is that tDCS will improve fatigue short- and long-term, and thus will improve quality of life (QOL) in recovered COVID-19 patients and that these changes will be associated with alterations in brain activity.

Aim 1: Determine the short-term effects of multiple sessions of M1 tDCS on fatigue, and the subsequent influence on QOL, in recovered COVID-19 patients.
Hypothesis 1: Fatigue and QOL will significantly improve immediately after five consecutive sessions of M1 tDCS.

Aim 2: Determine the long-term effects of multiple sessions of tDCS on fatigue and the subsequent influence on QOL, in recovered COVID-19 patients.
Hypothesis 2: The improvements in fatigue and QOL of recovered COVID-19 patients will be present at 3- and 6-week follow-ups.

Aim 3: Determine the association between cerebral glucose uptake and changes in fatigue/QOL measures in recovered COVID-19 patients.
Hypothesis 3: Changes in cerebral FDG uptake will be correlated with improved fatigue and quality of life.

Aim 4: Determine the effects of multiple sessions of tDCS on vascular function (arterial stiffness, endothelial function), baroreflex function, and cognitive function in recovered COVID-19 patients.
Hypothesis 4: Improvements in vascular function (arterial stiffness, endothelial function), baroreflex function, and cognitive function immediately after five consecutive sessions of M1 tDCS, and at 3 weeks and 6 weeks.

I.6 ***Background and significance and/or Preliminary studies related to this project. (do not indicate "see protocol")***

As of August 2020, the total number of COVID-19 cases has reached over 5 million nationwide with over 2.5 million recoveries and 160,000 deaths in the US. In Iowa alone, there have been over 47,000 cases, 900 deaths, and 35,000 recoveries. Currently, the immediate effects of COVID-19 are more emphasized than the long-term effects, such as fatigue and deconditioning. Certainly, it is important that healthcare providers monitor and manage the acute effects of COVID-19; but they should also ‘‘urgently prepare for. . . the more long-lasting aftershocks of the pandemic’’ [14]. Even after active COVID-19 cases dissipate, we may experience long-term health consequences for upwards of 12 years [15]. It is highly expected that the needs of COVID-19 survivors will signify a high burden of physical, neuropsychological, and social need following discharge. Specific data concerning the rehabilitation needs of this group is therefore urgently required. Thus, it is not premature to prepare for the time when incidence and death rates have reduced and the number of patients experiencing long-term symptoms that still affect their quality of life are increasing.

Previous coronavirus outbreaks have been associated with long-term symptoms like muscle weakness, pain, fatigue, depression, anxiety, pulmonary function impairment, vocational problems, and reduced quality of life [16-18]. Similarly, COVID-19 may have a lasting impact on physical, cognitive, mental, and social health, even in patients with mild disease presentation [19]. As acute symptoms improve and patients are exiting quarantine, they may be classified as hemodynamically stable and infection-free. Yet, many may still exhibit the physical (i.e., dyspnea, fatigue, weakness, pressure ulcers), cognitive (i.e., delirium), and emotional (i.e., depression) consequences of prolonged bed rest and quarantine, also known as post-intensive care syndrome [19]. These complications may lead to limited mobility, decreased independence in activities of daily living, re-hospitalization, and poor quality of life, all of which may be mitigated by early rehabilitation [20]. These lasting effects are also evidenced by recent studies [3,4] that assessed persistent symptoms in recently discharged COVID-19 patients and reported that decreased quality of life was observed among 44.1% and fatigue was still reported by 53.1% [3] to 71% [4] of patients. Importantly, both hospitalized and non-hospitalized patients showed persistent fatigue after acute COVID-19 infection [5].

Fatigue is “the decrease in physical and/or mental performance that results from changes in central, psychological, and/or peripheral factors” and significantly reduces one’s ability to participate in activities of daily living [21]. Many of the current treatments of fatigue, including pharmaceuticals, are only mildly effective and are often very expensive. Thus, a practical, inexpensive, and effective

adjunct treatment is urgently required. One possible modality that fulfills these requirements is transcranial direct current stimulation (tDCS) [22]. tDCS is a non-invasive means of increasing the excitability of targeted brain regions [9] and has been successfully used for several years in healthy populations [23] and in patients with neurological disorders to treat fatigue [24-27]. Recent studies have shown that tDCS intensities up to 4 mA are safe, tolerable, and do not elicit any serious adverse effects [24,28,29]. Additionally, tDCS can feasibly be delivered outside of a clinic setting [30], which may be of particular importance during a pandemic.

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

1. Docherty AB, Harrison EM, Green CA, et al; ISARIC4C Investigators. Features of 20 133 UK patients in hospital with COVID-19 using the ISARIC WHO Clinical Characterization Protocol: prospective observational cohort study. BMJ. 2020; 369: m1985.
2. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. JAMA. 2020; 323(13):1239-z242.
3. Carfi A, Bernabei R, Landi F. Persistent symptoms in patients after acute COVID-19. JAMA. 2020; July 9.
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5. Townsend L, Dyer AH, Jones K, Dunne J, et al. Persistent fatigue following SARS-CoV-2 infection is common and independent of severity of initial infection. medRxiv, July 30, 2020.
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II. Research Team

II.1 ***Principal Investigator***

Name	E-mail	College
Thorsten Rudroff	thorsten-rudroff@uiowa.edu	College Lib Arts and Sciences

II. ***Team Members***
2

UI Team Members

Name	E-mail	College	Contact	Key Prsn	UI COI	VAMC COI	Consent Process Involvement	Deactivated
Thorsten Rudroff, PHD	thorsten-rudroff@uiowa.edu	College Lib Arts and Sciences	Yes	Yes	No		Yes	No
Andrew Bryant, MD	andrew-d-bryant@uiowa.edu	Carver College of Medicine	No	Yes	No		Yes	No
David Bushnell, MD	david-bushnell@uiowa.edu	Carver College of Medicine	No	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	No	Yes	No		No	No
Alexandra Fietsam, MS	alexandra-fietsam@uiowa.edu	Inst Clinical & Translational	Yes	Yes	No		Yes	No
Colin Gimblet, MS	colin-gimblet@uiowa.edu	College Lib Arts and Sciences	No	No	No		No	No
Michael Graham, MD, PHD	michael-graham@uiowa.edu	Carver College of Medicine	No	Yes	No		No	No
John Kamholz, MD, PhD, MD	john-kamholz@uiowa.edu	Carver College of Medicine	No	Yes	No		Yes	No

Shannon Lehman, BA	shannon-lehman@uiowa.edu	University Hospitals	No	Yes	No	No	No
Parren McNeely, MD	parren-mcneely@uiowa.edu	Carver College of Medicine	No	Yes	No	No	No
Yusuf Menda, MD	yusuf-menda@uiowa.edu	Carver College of Medicine	No	Yes	No	No	No
Gary Pierce, PHD, MS	gary-pierce@uiowa.edu	College Lib Arts and Sciences	No	Yes	No	Yes	No
Janet Pollard, MD	janet-pollard@uiowa.edu	Carver College of Medicine	No	Yes	No	No	No
Laura Ponto, PHD	laura-ponto@uiowa.edu	Carver College of Medicine	Yes	Yes	No	No	No
Emma Somers, BS	emma-somers@uiowa.edu	Graduate College	No	No	No	Yes	No
Amy Marie Stroud, MSN	amy-stroud@uiowa.edu	Carver College of Medicine	No	No	No	No	No
Samalya Thenuwara, High School	samalya-thenuwara@uiowa.edu	Carver College of Medicine	No	No	No	Yes	Yes

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:***
Faculty

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
Thorsten Rudroff, PHD	Yes
Andrew Bryant, MD	Yes
David Bushnell, MD	Yes
Justin Deters, MS	Yes
Lisa Dunnwald, MPH	Yes
Alexandra Fietsam, MS	Yes
Colin Gimblet, MS	No
Michael Graham, MD, PHD	Yes
John Kamholz, MD, PhD, MD	Yes
Shannon Lehman, BA	Yes
Parren McNeely, MD	Yes
Yusuf Menda, MD	Yes
Gary Pierce, PHD, MS	Yes

Janet Pollard, MD	Yes
Laura Ponto, PHD	Yes
Emma Somers, BS	No
Amy Marie Stroud, MSN	No
Samalya Thenuwara, High School	No

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

III. Funding/Other Support

II ***Funding Sources***
I.
1

Source Entered as Text	DSP Link	Type	Source	Grant Title	Name of PI on Grant
* Source is entered as text yes		UI Institutional Grant/Award	Carver COVID-19 Pilot Grant Program		
Source is entered as text no		Departmental / PI Discretionary			
Source is entered as text no		Educational Institutions/Hospitals ↪ *Federal Agency*	Medical University of South Carolina *US Department of Health & Human Services, National Institutes of Health*	tDCS Treatment of Post-COVID-19 Fatigue	Thorsten Rudroff

* new source name

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
Thorsten Rudroff, PHD	No
Andrew Bryant, MD	No
David Bushnell, MD	No
Justin Deters, MS	No
Lisa Dunnwald, MPH	No
Alexandra Fietsam, MS	No
Colin Gimblet, MS	No
Michael Graham, MD, PHD	No
John Kamholz, MD, PhD, MD	No
Shannon Lehman, BA	No
Parren McNeely, MD	No
Yusuf Menda, MD	No
Gary Pierce, PHD, MS	No
Janet Pollard, MD	No
Laura Ponto, PHD	No
Emma Somers, BS	No
Amy Marie Stroud, MSN	No
Samalya Thenuwara, High School	No

III.5 ***What is the current status of this funding source?***

Source	Status	Other Status Description
Carver COVID-19 Pilot Grant Program	Awarded	

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)?***
Yes

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.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?***
150

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

VI.3 ***What is the age of the oldest adult subject?***
80.0

VI.4 ***What is the percentage of adult male subjects?***
50

VI.5 ***What is the percentage of adult female subjects?***
50

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***

- Fifty post-acute COVID-19 men and women with enduring fatigue will be recruited into one of two groups (tDCS or sham, n = 25 in each group), 50 post-acute COVID-19 men and women without enduring fatigue will be recruited into one of two groups (tDCS or sham, n = 25 in each group), and 50 subjects with no history of a COVID-19 diagnosis (controls) will be recruited into one of two groups (tDCS or sham, n = 25 in each group). For the COVID-19 subjects (fatigue and without fatigue), only those that are discharged from the UIHC COVID-19 inpatient clinic and/or that meet the CDC guidelines for discontinuing home isolation (i.e., fever-free for at least 24 hours, all symptoms improved after 10 days) will initially be

considered as long as they meet the rest of the following criteria:

Inclusion criteria (COVID-19 fatigue subjects):
• 18–80 yrs.

• Previous positive COVID-19 test

• >30 days since positive COVID-19 diagnosis

• Meet CDC guidelines (https://www.cdc.gov/coronavirus/2019-ncov/hcp/duration-isolation.html) for discontinuation of home isolation

• Meet the criteria for fatigue, based on the Chalder Fatigue Scale CFQ-11 case definition of fatigue

• Healthy enough to complete the protocol based, on information obtained from a clinical exam and past medical history, such as cardiovascular disease.

• Comprehension of the protocol, as indicated by an ability to respond to questions about the study after reading the consent form.

• Able to use and be contacted by telephone

• Able to speak, read, and understand English, and complete questionnaires in English

Exclusion criteria
• Medical diagnosis or condition that is considered to be an absolute or relative contraindication to participating in exercise training, such as major renal, pulmonary, hepatic, cardiac, gastrointestinal, HIV, cancer (other than treated basal cell cancer), or neurological disorders

• History/presence of secondary conditions such as seizure disorders (or on medications known to lower seizure threshold), hydrocephalus, diabetes mellitus, or claustrophobia

• Alcohol dependence or abuse (>2 drinks/day), or present history of drug abuse (last six months)

• History of significant traumatic brain injury or hydrocephalus

• Pregnancy

Inclusion criteria (COVID-19 non-fatigue subjects):
• 18–80 yrs.

• Previous positive COVID-19 test

• >30 days since positive COVID-19 diagnosis

• Meet CDC guidelines (https://www.cdc.gov/coronavirus/2019-ncov/hcp/duration-isolation.html) for discontinuation of home isolation

• Do not meet the criteria for fatigue, based on the Chalder Fatigue Scale CFQ-11 case definition of fatigue

• Healthy enough to complete the protocol based, on information obtained from a clinical exam and past medical history, such as cardiovascular disease.

• Comprehension of the protocol, as indicated by an ability to respond to questions about the study after reading the consent form.

• Able to use and be contacted by telephone

• Able to speak, read, and understand English, and complete questionnaires in English

Exclusion criteria
• Medical diagnosis or condition that is considered to be an absolute or relative contraindication to participating in exercise training, such as major renal, pulmonary, hepatic, cardiac, gastrointestinal, HIV, cancer (other than treated basal cell cancer), or neurological disorders

• History/presence of secondary conditions such as seizure disorders (or on medications known to lower seizure threshold), hydrocephalus, diabetes mellitus, or claustrophobia

• Alcohol dependence or abuse (>2 drinks/day), or present history of drug abuse (last six months)

• History of significant traumatic brain injury or hydrocephalus

• Pregnancy

Inclusion criteria (control subjects):
• 18–80 yrs.

• Healthy enough to complete the protocol based, on information obtained from a clinical exam and past medical history, such as cardiovascular disease.

• Comprehension of the protocol, as indicated by an ability to respond to questions about the study after reading the consent form.

• Able to use and be contacted by telephone

• Able to speak, read, and understand English, and complete questionnaires in English

Exclusion criteria
• Medical diagnosis or condition that is considered to be an absolute or relative contraindication to participating in exercise training, such as major renal, pulmonary, hepatic, cardiac, gastrointestinal, HIV, cancer (other than treated basal cell cancer), or neurological disorders

• History/presence of secondary conditions such as seizure disorders (or on medications known to lower seizure threshold), hydrocephalus, diabetes mellitus, or claustrophobia

• Alcohol dependence or abuse (>2 drinks/day), or present history of drug abuse (last six months)

• History of significant traumatic brain injury or hydrocephalus

• Pregnancy

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)***
A patient search was completed using TriNetX. On 2 Sept 2020, there were 42,530 registered COVID-19 patients at UIHC. Given that previous research has indicated that 53% - 71% of recovered patients still experience persistent fatigue, our potential subject pool would consist of 22,500+ people, of which we will only seek to recruit 100. The control subjects will likely come from the student and employee pools from UI and UIHC. Our experience indicates that recruiting 50 subjects will not result in any undue burdens.

VI.15 ***Describe how you will have access to each of your study populations in sufficient number to meet your recruitment goals.***
Prospective participants will be recruited from the University of Iowa Hospitals and Clinics, Iowa City, IA, via advertisements throughout the university campus and community, mass email to the university staff, faculty and alumni (>35,000 recipients), and from the 'volunteer research' link on the clinical trials webpage on the University of Iowa Hospitals and Clinics website (https://uihc.org/clinicaltrials/). Other main recruiting tools will include advertisements in local newspapers (Iowa City Press Citizen, Cedar Rapids Gazette) and Noon News publications in the University of Iowa Hospitals & Clinics daily newsletter, which is available to the public and patients at various locations in the hospital. Drs. Bryant, Gill, and Kamholz will also assess interest and provide referrals from visitors/patients in their clinics.

VI.16 ***Do you <u>plan</u> 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)?***

- Other UI campus site - Department of Health and Human Physiology, Integrative Neurophysiology Laboratory; Pappajohn Biomedical Discovery Building (PBDB);
- UIHC - Department of Neurology; Department of Internal Medicine (COVID-19 Home Treatment Clinic); PET Imaging Center; Iowa Translational Vascular Physiology Lab (Dr. Gary Pierce PI) in C204 GH

VII.A.2 ***Is this project also being conducted by other researchers at their own sites (e.g. a multi-site collaborative project)?***
Yes

VII.A.3 ***What is the UI site's role(s) for this project (check all that apply)?***

- Clinical/participating site

VII.A.10 ***What are collaborating site roles for this project?***

- Other - MUSC is the pilot grant organization for the study.

VII.B. Project Description (B)

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

- ☑ **Interventional** – Includes **Clinical (or Treatment) trial**, **Physiology intervention/study**, **Behavioral intervention/study**, **Diagnostic Trial**.
- ☑

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)

- ☑

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).

- ☑

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)

- ☑

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)

- ☑

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.1.c ***What is the last date the final subject/participant will undergo an intervention (i.e. the last study visit by any subject) as required by the protocol?***
05/26/2023

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 the evaluation, or testing, of 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 in a locked cabinet in the laboratory of the PI.

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. See attachments "tDCS Safety" and "tDCS Tolerability."

VII.B.32 ***Provide a summary of prior investigations with this device.***
The PI used this device in previous studies without any serious adverse side effects.

Workman CD, Kamholz J, and Rudroff T (2020). Transcranial Direct Current Stimulation (tDCS) for the Treatment of a Multiple Sclerosis Symptom Cluster. Brain Stimulation 13(1), 263-264.
Workman CD, Kamholz J, and Rudroff T (2020). The Tolerability and Efficacy of 4 mA Transcranial Direct Current Stimulation on Leg Muscle Fatigability. Brain Sciences 10(1), 12. IF: 3.332
Workman CD, Kamholz J, and Rudroff T (2020). Increased Leg Muscle Fatigability During 2 mA and 4 mA Transcranial Direct Current Stimulation over the Left Motor Cortex. Experimental Brain Research 238(2), 333-343.
Workman CD, Ponto LLB, Kamholz J, and Rudroff T (2020). No Immediate Effects of Transcranial Direct Current Stimulation at Various Intensities on Cerebral Blood Flow in People with Multiple Sclerosis. Brain Sciences 10(2), E82. IF: 3.332
Workman CD, Fietsam AC, Uc EY, and Rudroff T (2020). Cerebellar Transcranial Direct Current Stimulation in People with Parkinson's Disease: A Pilot Study. Brain Sciences 10(2), 96. IF: 3.332
Workman CD, Fietsam AC, and Rudroff T (2020). Transcranial Direct Current Stimulation at 4 mA Induces Greater Leg Muscle Fatigability in Women Compared to Men. Brain Sciences 10(4), 244. IF: 3.332
Workman CD, Fietsam AC, and Rudroff T (2020). Tolerability and Blinding of Transcranial Direct Current Stimulation in People with Parkinson's Disease: A Critical Review. Brain Sciences 10(7), 467. IF: 3.332
Workman CD, Fietsam AC, and Rudroff T (2020). Different Effects of 2 mA and 4 mA Transcranial Direct Current Stimulation on Muscle Activity and Torque in a Maximal Isokinetic Fatigue Task. Frontiers in human neuroscience 14, 240.

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 PI currently has several studies that have recently been approved by the IRB:

202006616
201912430
202002425
202005124
201905826
201905825

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 -

VII.D.1.a ***Will any of the materials/methods below be used by researchers (or their colleagues) to recruit subjects into this study?***

- ***the potential subject is a patient OR***
- ***use of any information considered to be Protected Health Information (PHI) OR***
- ***review of patient/clinic records be used in recruiting subjects***

- Yes

VII.D.1.b ***Describe source of records***
Patient information contained in charts available to the Neurology Clinic and COVID-19 Home Treatment Clinic at UIHC

VII.D.1.c ***Select all Private Identifiable Information (PII) or Protected Health Information (PHI) accessed and used for this study (select all that apply)***

Identify types of PHI accessed

Type of PHI	Data source
Name	☑
Street address	☑
City	☑
County	☐
Precinct	☐
Zip code	☑
Geocodes smaller than state	☐
Date of birth, ages > 89 years of age	☑
Diagnosis dates	☑
Procedure dates	☐
Admission or discharge dates	☐
Telephone numbers	☑
Fax numbers	☐
E-mail addresses	☑
Social Security number	☐
Medical record number	☐
Health plan beneficiary or account numbers	☐
Certificate/license numbers	☐
Vehicle identifiers and serial numbers or license numbers	☐
Device identifiers or serial numbers	☐
Web URLs	☐
Internet Protocol (IP) address numbers	☐
Biometric identifiers including finger/voice prints	☐
Full face photographic images or any comparable images	☐
None of the above	☐

VII.D.2.a ***List ALL of the variables, including any identifiers not previously entered or links to identifiers you plan to obtain/use for purposes of this study. (The information accessed should be the minimum data variables necessary for performing the desired analysis.)***
Patient's name
Patient's age
Patient's medical record number
Patient's phone number
Patient's email address

VII.D.3 ***Describe why you could not practicably recruit subjects without access to and use of the information described above***
The patients in this study will have recovered from COVID-19 and the Neurology Clinic and Home Treatment Clinic are our primary contact sources for recruitment. Therefore, Drs. Kamholz and Bryant, and their teams, may need to access their charts to help determine their suitability before

approaching them.

Additionally, the information in the phone script/screening questionnaire is required to determine eligibility for study participation.

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 recovered from COVID-19, without access to records we would only have less efficient ways of determining potential subjects to approach.

Directly screening potential participants with the screening questionnaire is also the most efficient and effective means of recruiting eligible participants.

VII.D.5 ***Describe plans to protect the identifiers from improper use or disclosure***
Patient data will be accessed only by authorized personnel, including Drs. Kamholz, Bryant, Rudroff, Workman. Data derived from the studies outlined in this proposal will be de-identified and then 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.

Paper copies of completed screening questionnaires will also be kept in a locked cabinet in Dr. Rudroff's laboratory.

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

The screening questionnaire for those that pass screening will be destroyed once the study is completed. Questionnaires for those that do not pass will be destroyed immediately via the secure/locked paper destruction bins located throughout the Field House building.

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 C204 GH Iowa Translational Vascular Physiology lab (HHP). Consent will be obtained in a private room with the doors closed. Consent may also be obtained via Zoom meeting or phone call prior to the Visit 1, where the staff may review the consent with potential participant over Zoom or phone and answer all questions by the participant. Participant may then sign the consent document at the end of the Zoom or phone call and either scan email a copy or bring the signed consent with them to Visit 1.

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:***
Approved laboratory staff will explain and discuss the protocol (via the screening questionnaire) with potential subjects over the phone before the subjects will be invited to the INPL and Iowa TVPL.

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

Name	Consent Process Involvement
Thorsten Rudroff, PHD	Yes
Andrew Bryant, MD	Yes
David Bushnell, MD	No
Justin Deters, MS	Yes

Lisa Dunnwald, MPH	No
Alexandra Fietsam, MS	Yes
Colin Gimblet, MS	No
Michael Graham, MD, PHD	No
John Kamholz, MD, PhD, MD	Yes
Shannon Lehman, BA	No
Parren McNeely, MD	No
Yusuf Menda, MD	No
Gary Pierce, PHD, MS	Yes
Janet Pollard, MD	No
Laura Ponto, PHD	No
Emma Somers, BS	Yes
Amy Marie Stroud, MSN	No
Samalya Thenuwara, High School	Yes

VII.D.15 ***Check all materials that will be used to obtain/document informed consent:***

- Consent Document

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 attachments:
tDCS_COVID19_ScreeningQ (to determine overall eligibility, including tDCS safety)
Chalder Fatigue Scale (to determine if the patient has persistent fatigue)
C19-YRS-Covid-Rehab-screening-tool (to determine if the subject is still experiencing problems from their illness)

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?***
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 will be recruited from the University of Iowa Hospitals and Clinics (Drs. Kamholz and Bryant), through advertisements on UIOWA Campus (including mass emails), and via individual emails (see attached template). Consent and enrollment procedures will be performed in the INPL (Director: Thorsten Rudroff, PhD, FACSM). Interested individuals will perform an initial phone screening

via questionnaires. Contact information for the prospective participants will be accessible only to the research staff according to HIPPA regulations. After completion of the phone screening, INPL personal will schedule the participants' first visit.

During the first visit, the PI or research staff will provide potential subjects with the consent summary and full consent document. Subjects will be allowed to review the documents at their leisure and research personnel will answer all questions asked by the potential subject. The potential subject will be informed of all potential risks before 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 for any reason. Consent may also be obtained via Zoom meeting or phone call prior to the Visit 1. After participant has been deemed eligible to participate in the study, research staff will conduct a zoom or phone call to walk through the study design and consent, as well as answer any questions the participant may have. Participants will then schedule their first five visits. After participants confirm their visit dates/times, they will be sent a confirmation email with detailed information about their visits, as well as a link to the consent form. Participant may then sign the consent document at the end of the Zoom or phone call and either scan email a copy or bring the signed consent with them to Visit 1.

During all study visits, all recommended precautions for mitigating the spread of COVID-19 during in-person research visits (e.g., face masks, face shields, extra cleaning before and after study visits, increased handwashing/sanitizing) will be followed as approved by our Departmental Executive Officer (DEO).

Mass emails to the University of Iowa and UHIC communities will be used to recruit participants who had a positive COVID-19 test 3 months or longer ago and who are either still having symptoms of post-COVID fatigue or are asymptomatic.

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, and upon request by the subject, the participant will be informed about the stimulation condition they experienced.

VII.E.2 ***Describe randomization scheme/assignment including ratio such as 1:1, 2:1 etc.***
The study will be a double-blind, sham-controlled, randomized parallel design. Post-COVID-19 patients with fatigue, post-COVID-19 patients without fatigue, and subjects without a history of a COVID-19 diagnosis (controls) will be randomly assigned to one of two groups. One group will

receive tDCS (tDCS Group; n = 25 in each group of subjects; 75 total) and the other group will receive SHAM (SHAM Group; n = 25 in each group of subjects; 75 total). The study will involve nine sessions at the INPL.

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)***
Chalder Fatigue Scale
C19-YRS-Covid-Rehab-screening-tool
Fatigue Assessment Scale (FAS)
Fatigue Severity Scale (FSS)
EQ-5D-5L Quality of Life questionnaire
Visual analog scale for pain
COVID19 Severity Survey
Pittsburgh Sleep Quality Index (PSQI) (to determine sleep quality)
International Physical Activity Questionnaire (IPAQ) (to quantify recent physical activity levels)

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***

Symptomatic subjects will be asked to complete 7 lab study sessions. The first lab session will take approximately 3.5 hours, the fifth lab session will take approximately 2 hours, and the tDCS sessions will take approximately 30 minutes. In all, full participation will take approximately seven weeks, with three week breaks between Lab Sessions 5, 6, and 7. Asymptomatic subjects will be asked to complete 1 lab study session, lasting approximately 2 hours.

Vascular study: In the initial session (Day 1) all subjects will 1) be consented, 2) undergo a blood draw to evaluate interleukin-6 values, lipids, glucose and c-reactive protein, complete. 3) pulse wave velocity testing (arterial stiffness); 4) carotid compliance/stiffness with ultrasound 5) brachial artery flow-mediated dilation (vascular endothelial function) 6) the Fatigue Assessment Scale (FAS), 7) the Fatigue Severity Scale (FSS), 8) the visual analog scale (VAS) for pain, 9) cognitive testing 10) 1-100 symptom scale, 11) international physical activity questionnaire (IPAQ), 12) Pittsburgh sleep quality index (PSQI), and 13) the 6-minute walk test. For asymptomatic participants, this will mark the end of their study participation. For

- symptomatic participants, they will then have their first round of the intervention receiving either sham or tDCS.

The following four days will include receiving either 20 min of tDCS or sham treatment, depending on group randomization. Day 5 will include the same testing battery (blood draw, PET scan in 10 subjects from each group [i.e., those that got the pre scan], questionnaires, fatigue testing, walking test) as Day 1, except the subjects will not repeat the MRI scan, strength testing, or receive tDCS.

LONG-TERM EFFECTS OF tDCS: Three- and six-weeks following Day 5, participants will repeat the testing battery conducted on Days 1 and 5.

BLOOD DRAW: Sessions 1 and 5 will begin at the hospital for the blood draw. CRU personnel will collect 5 mL of blood at the start of each session (total volume collected per participant: 5 * 2 = 10 mL) for interleukin-6 assays. After blood is collected, the participants will go to the Iowa Translational Vascular Physiology Lab (Dr. Gary Pierce PI) in C204 GH for non-invasive measurements of arterial stiffness,

endothelial function and cardiovagal baroreflex sensitivity(see below). Then, the participants will go to the INPL to proceed with stimulation and testing. After the assays are complete, the blood samples will be disposed of following standard Pathology procedures and eventually incinerated.

VASCULAR ENDOTHELIAL FUNCTION. Brachial artery flow-mediated dilation (FMD) using a 8-14 MHz linear transducer and ultrasound (Logiq 7, GE Healthcare) will be performed as a measure of vascular endothelial function. Briefly, while supine the subject's arm will be abducted and positioned comfortably on a side table and a pediatric cuff will be secured on the upper forearm (i.e., below the antecubital fold). After selecting a segment of the brachial artery ~3-6 cm above the antecubital fold with clear anterior and posterior intimal-luminal interfaces, the ultrasound probe will be clamped in place to avoid any involuntary movement. Baseline ECG-gated to R wave (i.e., end-diastolic) ultrasound images and Doppler flow velocity of the artery will be acquired in duplex mode (B Mode/Pulsed Doppler) simultaneously for 30 seconds. For FMD, brachial artery reactive hyperemia will be produced by inflating the pediatric forearm blood pressure cuff to 250 mmHg for 5 minutes followed by rapid deflation. ECG-gated end-diastolic ultrasound images and pulsed doppler of the brachial artery will be acquired during the last 30 seconds of the cuff occlusion and for two minutes after the release of the cuff. A commercially available software package (Vascular Analysis Tools 6.0, Medical Imaging Applications, LLC) will be used to acquire and analyze ECG-gated brachial artery diameters. Images will be digitalized and stored for later analysis on a personal computer. Brachial artery dilation will be determined as the % change and mm change from baseline. FMD is dependent upon the post-occlusion increase in hyperemic blood flow or shear stress.

ARTERIAL STIFFNESS. Carotid-femoral, carotid-brachial, and carotid-radial PWV will be measured non-invasively by recording carotid, femoral, brachial and radial artery pressure waveforms sequentially with an applanation tonometer (Non-invasive Hemodynamics Workstation, Cardiovascular Engineering, Inc.). Pressure waveforms are gated to the ECG R wave in order to calculate the transit time (t) between the foot of the carotid and the respective peripheral (femoral, brachial, radial) waveforms. The carotid-femoral transit distance (CFTD) is estimated between the 2 anatomical sites as the difference between the suprasternal notch (SSN) to carotid (SSN-C) and femoral (SSN-F) sites. Thus, the CFTD is calculated as CFTD= (SSN-F) - (SSN-C) and PWV calculated as CFTD/t. Next, carotid artery compliance and beta-stiffness index will be determined noninvasively by high-resolution ultrasonography (Logiq 7, GE Healthcare) of the right common carotid artery and contralateral assessment of carotid artery blood pressure via non-invasive carotid artery applanation tonometry respectively. Carotid artery diameters are measured ~2 cm proximal to the carotid bulb with the transducer placed at a 90° angle to the vessel by off-line analysis of DICOM images with image analysis software (Medical Imaging Applications, LLC). Maximal diameters (i.e. systolic expansion) and minimal diameters (i.e. diastolic relaxation) are measured in sync with carotid artery blood pressure waveforms. Carotid blood pressure waveforms are calibrated using diastolic and mean brachial artery blood pressure obtained from standard brachial artery cuff blood pressure.

CARDIOVAGAL BAROREFLEX SENSITIVITY. Baroreflex sensitivity will be determined by recording blood pressure via beat-to-to beat finger blood pressure (Finapres, AD Instruments Inc.) and heart rate using 3 lead ECG continuously for 15 minutes supine and BRS will be calculated using the sequence technique.

COGNITIVE TESTING: You will complete three cognitive tests, called the NIH Cognitive Battery Toolbox, that will assess your executive function, working memory, and processing speed. All tests will be completed using an iPad provided by the lab and will take approximately 15 minutes total.

1-100 SYMPTOM SCALE: You will be asked to fill out a survey rating each of your COVID-19 symptoms individually on a scale from 0-100. Symptoms include chest pain, chills, diarrhea, dizziness/vertigo, dry cough, dry eyes, dry mouth, fatigue, fever over 100.3*F, headache, lack of appetite, loss of smell/taste, muscle or body aches, nasal congestion or runny nose, nausea or vomiting, shortness of breath, sore joints, and sore throat. These scores will be totaled and averaged for overall symptom severity.

PHYSICAL ACTIVITY: Participants will be asked to fill out short survey called the International physical activity questionnaire (IPAQ) to quantify job-related and leisure-time physical activity and sitting time over the past 7 days.

SLEEP QUALITY: Participants will fill out the Pittsburgh sleep quality index (PSQI) survey to determine sleep quality over the past month.

STRENGTH TESTING:
Knee extension/flexion will be performed in a sitting position. The range of motion will be between 100° and 0° of flexion. The axis for extension/flexion is assumed to be a horizontal line through the femoral condyles. The subject will be secured with Velcro bands to help isolate the knee joint. The isokinetic measurements will be performed with 3 maximal extension/flexion repetitions at 30º/s. In addition, three repetitions of isometric tests performed at 65° (extensors) and 30° (flexors) of knee flexion will also be obtained. All testing will be completed on both legs and the highest torque obtained from the three repetitions will be used to determine the weaker leg. The M1 that controls the weaker leg will serve as the anodal brain target for tDCS.

ISOKINETIC FATIGUE TEST: Subjects will perform 40 consecutive repetitions of isokinetic concentric/concentric flexion and extension of the knee on the stronger leg at 120º/sec. The weaker leg fatigue task will be completed in the same manner immediately after the stronger leg.

6 MINUTE WALK TEST (6MWT): The subjects will be led to a cordoned-off hallway to perform the walk. Subjects will be instructed to walk at their normal, usual pace back and forth between two points separated by 30 m for 6 min. Gait characteristics and distance walked will be calculated and recorded.

tDCS TREATMENT 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 positive electrode (anode) will be placed over the M1 representation of the weaker leg (as determined by the strength test), and the return electrode (cathode) will be placed above the eyebrow on the opposite side of the head.

tDCS BLOCK: The participants will receive tDCS for 20 min while seated comfortably and quietly in a room. The intensity will start at 0 mA and will be incrementally increased to the target intensity of 4 mA over the initial 30 seconds. At the 20-minute time point, the current will be gradually reduced to 0 mA over 30 seconds.

SHAM BLOCK: During the sham block, stimulation will ramp up over 30 seconds, remain at the target intensity for 30 seconds, and then will ramp down over 30 seconds during the first and last 90 seconds of the 20 minute stimulation period. This sham protocol has previously been shown to improve subject blinding integrity.

Brain activity PET Imaging with [18F]Fluorodeoxyglucose (FDG): A subset of 10 subjects from each group will be asked to fast for a minimum of 6 hours prior to the FDG administration. The blood glucose level will be checked and must be less than or equal to 200 mg/dL in order to proceed with the imaging. FDG (5 mCi ± 10% IV) will be administered and tracer uptake will take place in a quiet, darkened room with eyes open and ears unplugged. Attenuation correction imaging (either AC-CT or transmission imaging) will be performed with emission imaging equivalent to that used in the ADNI-3 protocol.

FDG PET Image Processing: FDG images will be analyzed by volume-of-interest (VOI) based on the individual's structural MRI (maximum probability atlas of Neuro Tool of PMOD Biomedical Image Quantification, version 4.1, PMOD Technologies, Ltd., Zurich, Switzerland) as well as using currently-available software tools designed specifically for the analysis of FDG images (e.g., NeuroQ (Syntermed, Inc.), PALZ (PMOD Technologies, LTD), MIM6, Neuro tool (v.6.6, MIM Software, Inc.). Partial volume-corrected image data will also be analyzed. Global metabolism will be determined by calculating the volume-weighted average of the standardized uptake values (SUV) of the intracerebral pixels. Mean, median and partial volume-corrected mean SUVs will be determined for each tissue type (GM, WM), lobe, and region using the Neuro Tool (PMOD).

MRI: MR imaging will be conducted on a GE 750W 3T scanner using a 32-channel head coil. Anatomical images will include volumetric sagittal T1 MPRAGE (TI=900ms, TE=3.2ms, TR=8.5ms, flip angle=8%;, FOV=256x256x192mm, matrix=256x256x192, bandwidth= 250Hz/pixel, acceleration=2) and sagittal T2 CUBE (TE= 60ms, TR= 2500ms, echo train length=140, FOV=256x256x192mm, matrix=256x256x192, bandwidth=500Hz/pixel, acceleration=2) scans acquired using prospective motion correction (PROMO) and a 1.0 mm isotropic spatial resolution.

Questionnaires and physical testing (e.g., strength/fatigue) will be performed in the INPL. PET scanning will either start in PET Imaging Center (height/weight measurements, glucose/pregnancy testing, IV insertion) and then walk/wheelchair the subjects to PBDB (FDG administration, uptake, and PET scanning), or be exclusively performed in PBDB (to accommodate any potential UIHC research

restrictions) at the discretion of PET Imaging staff. MRI scans always take place in the research dedicated 3T MRI scanner in PBDB.

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***
Yes

VII.E.17 ***Describe:***
Participants will receive parking vouchers for UIHC parking ramps for the duration of their visits.

VII.E.18 ***If you plan to compensate subjects using cash, checks or cash equivalent does your unit have a Cash Handling Procedure in place that has been approved by Accounting Services?***
Yes

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

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

- Subjects who are part of the symptomatic group will be compensated $120 for their time and effort upon completion of the first five visits of the study. Two follow-up visits will be compensated at $25 per visit, for a total of $170 for completion of the entire study. If the subjects withdraw before completing the entire study, they will be paid for each session they completed, as follows: blood draw/vascular assessment, $30 each visit ($60 total for baseline and post-tDCS testing), tDCS/SHAM sessions: $15 each visit ($60 total).

  Subjects who are part of the asymptomatic group will be compensated $35 for their time and effort upon completion of visit one.

VIII. Risks

VIII.1 ***What are the risks to subjects including***
- emotional or psychological
- financial
- legal or social
- physical?
tDCS safety (only applicable to symptomatic participants): 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 is 0.011 mA/cm^2. In conclusion, 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.

Risk of Blood Draw: Subjects may experience some discomfort/bleeding from the blood draws. Other risks include bruising and infection. To minimize these risks, all blood draws will be performed by certified personnel at the CRU in the University of Iowa Hospital.
Carotid-femoral pulse wave velocity (PWV) and flow-mediated dilation: There are no known or foreseeable risks associated with the use of carotid-femoral pulse wave velocity or flow-mediated dilation. ECG electrodes may cause minor irritation to the skin.

Risks of performing motor tasks: There is potential for injury (muscle strain) resulting from the strength, fatigue, and walking tests. There is a 0.01% chance of death (in people who have heart problems), a 0.02% risk of cardiac arrhythmias that would require the subjects to go to the hospital (in people with heart problems), and a risk of an increase or decrease in blood pressure. Following participation, subjects may experience some muscle soreness. Muscle soreness tends to be more common for individuals who have not exercised recently. 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 15% of the dose that a medical radiation worker can accrue yearly. FDG dose = 5 ± 10% mCi. Radiation dose = 110 mrem/mCi = 605 mrem + 180 mrem for CT = 730 mrem = ~15% of dose for medical radiation worker. 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.

Risks of Pulse Wave Velocity

There are no known risks associated with the use of a non-invasive pulse transducer for pulse wave velocity. ECG electrodes may cause minor irritation to the skin.

Risks of Carotid Echocardiography
There are no known serious risks associated with the use of carotid echocardiography. ECG electrodes may cause minor irritation to the skin.

Risks of Brachial Artery FMD test
There is a risk of mild discomfort on the forearm when the blood pressure cuff is inflated and a mild temporary sensation of "pins and needles" in the forearm and hand. This feeling is completely reversed within several minutes after the cuff is released with no permanent discomfort.

Risk Cardiovagal Baroreflex Sensitivity test
There are no known risks associated with the use of this test.

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.

To minimize these risks involved in drawing blood, all blood draws will be performed by certified personnel at the CRU in the University of Iowa Hospital and Clinics. As pointed out by the Risks section, this is a physically minimal risk study and the main expected risk would be fainting from a blood draw. The safety plan is to have a registered nurse/phlebotomist there at all times during the blood draw. This RN/phlebotomist will position the participant for the blood draw in a seated or recumbent (lying) position. The nurse/phlebotomist will monitor for signs of fainting during the blood draw, such as dizziness, confusion, pallor, nausea and/or sweaty palms. If present, the nurse/phlebotomist would stop the procedure assist the participant to try to get their legs above their heart or lie down with legs elevated. In the event of a fainter, the nurse/phlebotomist would follow basic first aid put them in a laying position with their legs above their head and loosen any constrictive clothing. The participant would be monitored for pulse and breathing. Any other events would be unexpected and handled as deemed appropriate, by CRU personnel.

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)?***
Subjects may experience some fatigue improvement from participation, but it is not expected that the protocol will cause long-term or curative results.

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 fatigue rehabilitation for people who have persistent fatigue from COVID-19 infection.

X. Privacy & Confidentiality

X.1 ***What are you doing to protect the privacy interests of the subjects?***
All interactions (in person, over the phone) with subjects will be in a private room (i.e., room N414 of the Field House) and at a time when 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):***

- 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 only to current laboratory staff.
- Electronic records (computer files, electronic databases, etc.) - All data collected, including personal identifiable information, will be stored electronically on University of Iowa secured networks (i.e., the rdss/Research Data shared drive) with access restricted to the current investigators.
  - Name - Bryan Ringen
  - Title - IT Support Consultant
  - University Job Classification - Faculty/Staff
- Biologic samples (blood draws, check swabs, saliva samples, tissue samples, etc.) - Biologic samples (blood draws, check swabs, saliva samples, tissue samples, etc.) - Cru staff will draw blood, place a patient identifier label (zebra sticker) on the PST tube, place in a bio-hazard bag and hand deliver the specimen to UIDL staff. Specimens will be delivered by CRU personnel to Specimen Control (also known as Technical Services). Upon receipt, core lab personnel will accession the specimen into Epic. Please note that the core laboratory is staffed 24/7, 365 days a year and has restricted access. Specimens are processed and temporarily stored, securely, prior to testing. After the completion of testing, specimens are discarded as biological waste. All biological waste is eventually incinerated.
  - Name - Matthew Krasowski
  - Title - Clinical Professor
  - University Job Classification - Faculty/Staff

X.5 ***Do the confidentiality protections indicated above allow only members of the research team to access the data/specimens?***
No

X.6 ***Describe***
The data that will be shared with the Medical University of South Carolina (MUSC) will be de-identified, age, race and ethnicity will be reported as required by NIH (see attached template that will be requested for reporting purposes) as part of a final report to MUSC.

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***
The generalized estimating equation (GEE) framework will be utilized to assess changes over time in fatigue and quality of life measures. An interaction term between time and treatment will allow us to test the within- and between-treatment differences over all time points. Using histograms, variable distributions will be assessed to decide which link function to specify when modeling each outcome. To account for the inherent correlation that occurs in repeated measures data, we will cluster on subject ID. In addition to

examining the unadjusted relationship between the time-treatment interaction and each outcome, we will consider the addition of control variables, which will reduce the likelihood of unaccounted confounders. The control variables being considered for inclusion in the adjusted models are age, sex, and disease duration. For each outcome, models will be fit for all possible combinations of control variables. The predictor set that yields the smallest Akaike information criterion (AIC) will be considered the optimal control variable set to adjust associations between the main predictor and the outcomes. Statistical significance will be assessed at the α = 0.05 level.

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

The sample size calculation was based on the Fatigue Severity Scale data from our own preliminary data that assessed the effects of multiple sessions of 4 mA tDCS on fatigue in people with multiple sclerosis. The effect size of this difference = 0.91 (Cohen's d). With alpha fixed at 0.05, we would need 20 total subjects in each group (tDCS and SHAM; details below) to achieve 80% power in a two-tailed independent samples test. Therefore, to account for 20% data and subject attrition, we will recruit 25 subjects per group (150 total).

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 the 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