Mass General Brigham

Institutional Review Board
Intervention/Interaction Detailed Protocol

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Project Title: Home-Based transcranial direct current stimulation (tDCS) for treatment of cognitive post-acute sequelae of COVID-19 (PASC)

Version Date: 05/05/2023

For Intervention/Interaction studies, submit a Detailed Protocol that includes the following sections. If information in a particular section is not applicable, omit and include the other relevant information.

1. Background and Significance

The COVID-19 pandemic has posed vexing challenges for healthcare systems worldwide. As of September 2021, over 220 million people have been infected with SARS-CoV-2 around the globe[1].

While SARS-CoV-2 infection can cause severe respiratory symptoms in the acute phase, a significant portion of the patients, even those with mild respiratory symptoms, experience neuropsychiatric complications[2-4]. Importantly, these symptoms can be present months after the respiratory symptoms are resolved, as part of the post-acute sequelae of COVID-19 (PASC)[5]. Cognitive deficits in particular have been widely reported including in patients with mild infection[6, 7].

A study investigating the long-term effects of SARS-CoV-2 infection found that 34% of the hospitalized patients continue to experience short-term memory problems and 28% reported attentional deficits, which is consistent with early reports indicating 36% of patients with severe infection demonstrating “dysexecutive syndrome”[2]. Pharmacological options that are used to mitigate these symptoms are limited[8, 9]. Therefore, alternative therapeutic methods are urgently needed.

Noninvasive neuromodulation therapies are part of the standard of care for several neuropsychiatric conditions. Transcranial Direct Current Stimulation (tDCS), a form of noninvasive neuromodulation, was shown to improve executive deficits in patients with ADHD, by enhancing a specific EEG biomarker (i.e., treatment target)[10]. The most common cognitive deficits in PASC mirror those typically described in ADHD[7]. Home-based tDCS has been established as a feasible, safe and effective treatment[11], and may be particularly well-suited to improve cognitive deficits associated with PASC.

In this study, we will conduct a sham-controlled pilot feasibility trial of a 4-week home-based tDCS therapy to improve sustained attention, processing speed and inhibition in patients experiencing dysexecutive deficits following SARS-CoV-2 infection.

2. Specific Aims and Objectives

Aim 1. Determine the feasibility of home-based tDCS treatment in COVID-19 patients.

> Hypothesis 1. The proposed treatment will be feasible as reflected in patients' adherence to the protocol (dropout rate and compliance).

Aim 2. Determine the immediate and long-term cognitive effects of anodal tDCS to the left dorsolateral prefrontal cortex (DLPFC) in COVID-19 patients.

> Hypothesis 2. Patients in the tDCS group will show greater improvement at Week 4 in markers of executive function (processing speed and inhibition) relative to the sham group. The tDCS group will continue to perform better (relative to sham) at Week 8 (4 weeks after the last treatment).

Aim 3. Determine the physiological effects of anodal tDCS to the left DLPFC in COVID-19 patients.

> Hypothesis 3. Patients in the tDCS group will show greater increase in P300 amplitudes at Week 4 relative to the sham group. The improvement in processing speed and inhibition from baseline to Week 4 in the tDCS group will correlate with the change in P300 EEG amplitude. The improvement will be maintained at Week 8.

3. General Description of Study Design

In our study, we will test our hypotheses using a parallel, placebo-controlled design, in which each patient will be randomly assigned to either the active or sham tDCS group. Patients will self-administer tDCS for 30 minutes daily for 4 weeks. We will assess patients' behavioral performance and neurophysiology in 4 study visits to the Martinos Center (baseline, week 1, week 4, and week 8).

4. Subject Selection

We will enroll 40 adult patients diagnosed with PASC. 20 patients will receive active tDCS and 20 patients will receive sham tDCS.

Inclusion Criteria

1. Male and female outpatients 18-65 years of age
2. A diagnosis of PASC as indicated by past COVID-19 infection (confirmed with a PCR test), and subjective, persistent symptoms, which may include 'brain fog', confusion, short-term memory deficits, trouble concentrating, delirium, difficulties in multitasking, and inability to perform compared to baseline.

Exclusion Criteria

1. Contraindication to tDCS: history or epilepsy, metallic implants in the head and neck, brain stimulators, vagus nerve stimulators, VP shunt, pacemakers, pregnancy.
2. Active substance dependence (except for tobacco).
3. Pregnant or nursing females.
4. Inability to participate in testing procedures.
5. Premorbid neurological conditions (including neurovascular and neurodegenerative diseases such as traumatic brain injury, stroke, Parkinson's, AD and other dementias) and severe psychiatric disorders (bipolar disorder, schizophrenia), and ADHD.

Other notes
1. Comorbid psychiatric disorders will be allowed as long as clinicians believe that they are not the primary diagnosis for cognitive deficit. The exception will be substance dependence.
2. Concomitant, ongoing medications will be allowed, but subjects will be asked to remain on a stable dose.
3. Each subject must be judged capable of understanding the nature of this study, as well as the risks and potential benefits.

Patients will be recruited via referral from the MGH Neuropsychiatry post-COVID clinic and via community advertisement. A trained clinical research coordinator will be responsible for subject recruitment, and recruitment will primarily occur between October 2021 and April 2023.

5. Subject Enrollment

Potential subjects will be pre-screened over the phone for study eligibility using a standardized phone screening form. This screening form will request the potential subjects' ages, psychiatric & neurologic history, substance use history, as well as any potential contraindications to tDCS, such as metallic implants or seizure history. Trained study staff will record the answers in writing and will inform the potential subjects that their answers will be kept strictly confidential throughout the study. All screening forms referring to potential subjects who are noted to be ineligible for our study will be properly disposed of as per Massachusetts General Hospital guidelines.

Potential subjects who are determined to be eligible for the study based on the phone screening will be invited to visit the Martinos Center for consenting. Informed consent will be obtained prior to the performance of any protocol procedures by the PI, co-investigators or specifically trained study staff. The informed consent document will be used to explain in simple terms the risks and benefits of study participation to the subject. The nature of the study will be fully explained to the subject by the PI, co-investigators or specially trained research coordinators. The subject will be encouraged to ask questions pertaining to their participation in the study and the subject may take as much time as they feel necessary to consider his/her participation in the study as well as consult with family members or their physicians. Participation in this study is voluntary and the subjects may withdraw from the study at any time. The IRB-approved informed consent documents will be signed and dated by the subject and the person obtaining consent.

Participants must be capable of understanding the nature of this study, its potential risks, discomforts, and benefits. Since all participants will be 18 or older, they will provide consent without parental or other guidance. Informed consent will be obtained after the study purpose and procedures have been fully and clearly explained, and the potential participant has

demonstrated an understanding of the protocol, willingness to participate, and capacity to consent.

Randomization

A randomized order of numbers from 1-40 will be generated using the *randperm* function in Matlab (Natick, MA, http://www.mathworks.com/), An example is illustrated below:

32	40	22	34	35	6	3	16	11	30	33	7	38	28	17	14	8	5	29	21
25	37	31	27	26	19	15	1	36	23	2	4	18	24	39	13	9	20	10	12

These numbers represent the IDs corresponding to the enrolled participants assigned based on enrollment order (e.g., 1 represents the first enrolled subject). In principle, the subjects whose IDs are in the first line will be assigned to the active tDCS group, while those with IDs from the second line will be assigned to the sham tDCS group. A Matlab script will continuously monitor the age and gender distribution of the enrolled subjects and recompute the random order for the remaining subjects to ensure that the groups are matched for age and gender.

6. STUDY PROCEDURES

At-Home tDCS – General Information

Recent advances in tDCS devices and headgear have made it possible for individuals to self-administer tDCS in remotely supervised sessions. Detailed guidelines for home-based tDCS delivery have been established and the protocol has been tested in patient populations [11, 12]. Our tDCS protocol will follow these guidelines.

Study staff, after being briefed on the contraindications to tDCS and relevant screening procedures, will be trained on the correct placement of the headset device, as well as the administration of the stimulation. All study staff will be familiar with, and have access to, guides that detail the steps necessary to activate and program the tDCS device.

Study Visit One (Baseline)

All patients will make their first study visit (baseline) within 3 days prior to Day 1 of tDCS. In this first visit, patients' tDCS tolerability will be tested and they will be provided with detailed instructions on how to use the device. Additionally, women of child-bearing potential will be asked to verbally confirm a negative pregnancy status. In an event where pregnancy status is uncertain, a pregnancy test will be taken to confirm a negative pregnancy status prior to initiation of study procedures.

tDCS Self-Administration Education

Prior to subject arrival and acquisition of the tDCS device, study staff will program the device to provide the current intensity, duration, and condition (active v. sham) for every session that is planned. Study staff will additionally program the device to provide only the number & frequency of sessions detailed in the protocol.

Subjects will first view an instructional video that explains on a step-by-step basis each portion of tDCS application and administration.

Study staff will then ask the subjects to prepare and apply the headstrap portion of the device. This headstrap is essential to proper placement and maintenance of placement of the tDCS electrodes. For the current study, the anodal placement will be at the left DLPFC (F3 based on the international 10-20 EEG system), and cathodal placement will be at contralateral supraorbital region (FP2).

Study staff will then assess the contact quality before continuing. This step is necessary because the device will fail to unlock if impedance levels are too high, and we must ensure that subjects are able to achieve a sufficiently low impedance (<10 Ω) on their own before allowing them to stimulate themselves at home. Study staff will provide assistance on ways to help lessen the impedance, such as applying more saline solution to the electrodes, or moving hair away from the electrode contact points.

Subjects will then undergo a brief tDCS session to assess the tolerability of the stimulation. Subjects will first experience the full 2.0 mA anodal tDCS. If they cannot tolerate the 2.0mA dose, study staff will repeat the process with a 1.5mA dose and a 1.0mA dose. If the subject cannot tolerate a 1.0mA dose, they are excluded from participating further in the study.

Cognitive Assessment

At the baseline visit, several variables that may affect the response to tDCS will be collected: age, sex, education, time from illness onset. At the baseline visit, as well as future visits, the following computerized tasks included in the NIH Toolbox Cognition module will be administered by study staff to assess functioning in several cognitive domains: Dimensional Change Card Sort Test (set shifting), List Sorting Working Memory Test (working memory), Picture Sequence Memory Test (episodic memory), Oral Reading Recognition Test (Language), and Pattern Comparison Processing Speed Test (processing speed). Along with the Cognition battery, subjects will take the Assessment of Post-Acute Sequela of COVID-19 (A-PASC) Inventory during each study visit to assess the impact of their PASC-related symptoms on their day-to-day life.

Additionally, during this visit, subjects will complete the following computer task to assess their current executive functioning while their EEG is being recorded ([500 samples/sec; 64 channels; electroencephalography (EEG) system (Brain Vision, USA)]):

> Eriksen Flanker Task (EFT): This is a well-established experimental task to assess sustained attention, conflict monitoring and response inhibition. In the task, subjects must attend and respond to the direction of a central arrow that is surrounded (“flanked”) by distracting stimuli. The flanking arrows can either have the same or opposing orientation as the central one. Trials are classified as congruent, in which the central arrow points to the same direction as the flanker arrows, and incongruent trials, in which the central arrow points to the opposite direction of the flanker arrows. Subjects are instructed to press the left or right arrow buttons depending on the direction to which the central arrow was pointing at, ignoring the flanker arrows. The task consists of 140 trials in two blocks of 70, with 2 congruent trials for each incongruent trial, in order to build a tendency towards congruent responses and thus increase the difficulty of conflict

detection in incongruent trials. Subjects will perform 2 runs of the task. The accuracy of responses and the reaction time for each stimulus will be measured while also recording EEG data during the task. The stimulus onset and the subjects' responses will be time-stamped at the EEG data in order to later extract ERPs.

During this visit, subjects will undergo additional EEG recording prior to the EFT. EEG will be recorded for two minutes while their eyes are open, staring at a fixation cross, and for two minutes while their eyes are closed. Subjects will be reminded to remain still prior to each of these recordings. The purpose of this additional recording is to investigate potential resting-state deviations in the PASC population.

Demographics Questionnaire

At the baseline visit, participants will also fill out questionnaires related to demographics, education, occupation, ethnicity and handedness.

At-Home tDCS – Administration and Supervision

Subjects will, prior to engaging with the tDCS equipment, connect with a study staff member via a video-conference software. Participants will be supervised for the first five At-Home tDCS sessions as well as at the beginning of each week of stimulation. If the participant is comfortable after the weekly supervised session, the participant will independently administer tDCS until the following week. During supervised sessions, if subject does not have sufficient Internet access as to maintain the integrity of the conference call, participation will be discontinued. If the participant does not feel comfortable independently conducting tDCS sessions, daily remote supervision will continue until the subject is comfortable independently conducting tDCS sessions.

During supervised sessions, study staff will then monitor the application of the headstrap and ensure that the electrode sponges are in the correct locations (F3 and FP2 for anodal and cathodal placement, respectively). Subjects will report the contact quality, as measured by the tDCS device, to the study staff. Based on the quality, the study staff will either recommend solutions to improve impedance levels (double checking electrode placement, adding saline solution), or proceed with stimulation. Once the study staff deems the impedance an appropriately low level, they will provide the subject with the stimulation code that will unlock the tDCS device and allow it to begin stimulation.

Stimulation will last 30 minutes, along with a 15 second ramp-up to the target dose from 0mA, and a 15 second ramp-down back to 0mA after the 30 minutes stimulation. Subjects who are randomized to the sham group will experience the same 15 second ramp-up and ramp-down period to mimic the sensation of anodal tDCS, but the device will not provide current during the 30-minute stimulation period.

Fifteen minutes after stimulation begins, study staff will ask the subject how they are doing and will re-check proper electrode and headstrap placement via videoconference.

After stimulation concludes, participants will complete questionnaires designed to assess any side-effects due to the stimulation, as well as their energy levels and mood via REDCap. Subjects will be sent REDCap surveys via a secure email link. Email communication with

subjects will consist only of sending a secure REDCap link for the questionnaires, and will not be used to discuss personal health information. In the event that email must be used to discuss or send personal health information, Send Secure will be used to encrypt emails as per Partners Healthcare standards and subjects will be advised to create a login for this information. Non-secure communication will only be used at a subject's request. After supervised sessions, study staff will then plan the following day's stimulation time with the subject.

Study Visit Two

Approximately one week after beginning tDCS sessions, subjects will return to CNY for further assessments.

These assessments will consist of the same cognitive battery as Visit One, along with the same behavioral computer task. EEG will be collected during the computer task, as well as during rest.

Study Visit Three

Approximately four weeks after beginning tDCS sessions, subjects will return to CNY once more for further assessment.

These assessments will consist of the same cognitive battery as Visit One, along with the same behavioral computer task. EEG will be collected during the computer task, as well as during rest..

At conclusion of the day's tasks, the subject will return the tDCS device. Study staff will at this point be able to ascertain protocol adherence throughout the stimulation portion of the study by downloading data regarding stimulation frequency from the device.

Study Visit Four

Approximately four weeks after conclusion of tDCS daily sessions (about eight weeks after beginning tDCS sessions), subjects will return to CNY a final time for assessments.

These assessments will consist of the same cognitive battery as Visit One, along with the same behavioral computer task. EEG will be collected during the computer task, as well as during rest.

7. Risks and Discomforts

Risks Associated with Transcranial Direct Current Stimulation (tDCS):

tDCS is an investigational device that does not pose a significant risk to participants. The safety of this technique has been studied and summarized by different research groups around the world, especially in recent years[13-18]. Current safety guidelines are defined from a review of more than 18,000 stimulation sessions in more than 8000 subjects using low intensity stimulation (<4 mA; up to 60 min duration/day)[17].

In a comprehensive review of studies published from 1998 to 2008, it was concluded: "Extensive animal and human evidence and theoretical knowledge indicate that the currently used tDCS protocols are safe"[14]. Accordingly, we will strictly follow standard methodology for tDCS application and stimulation parameters that have been used in previous research studies. We will also exclude participants with unstable medical conditions, or any illness that may increase the risk of stimulation, for example epilepsy. Furthermore, subjects should have no metallic implants. All these elements will be considered in this study and are included in the informed consent. The protocol to be used will apply stimulation levels that fall within safety standards established by studies investigating neural tissue damage, as well as numerous studies applying tDCS to human participants. Human studies that reported safety outcomes have included patient populations and stimulation schemes of up to 6 weeks of daily stimulation[19]. No major adverse effects were reported using these parameters.

The electric field strength induced in the cerebral cortex using standard tDCS current densities (1-2 mA) is in the range of 0.4-0.8 V/m. For comparison, both the applied current and the electric field are approximately 1000 times smaller than those typically used in electroconvulsive therapy (ECT). Such small electric fields are lower than the threshold required to induce action potentials in the brain but may modify spontaneous neuronal firing rates[16,20].

Side Effects:

The most common side effects associated with tDCS according to the most recent data available[16,20,21] are:

1. Sensations reported by subjects under the electrode (these sensations can sometimes, though rarely, continue throughout the stimulation time and for a brief period following completion of the tDCS but usually resolve shortly after the initiation of tDCS): mild tingling, light itching, slight burning sensation, discomfort or mild pain.

2. Effects reported that occur only during tDCS: visual sensation during switching on and off the stimulation. Other effects that can occur both during and after tDCS include: moderate fatigue, skin redness, headache and difficulties in concentration.

Rare side effects:

1. Nausea

2. Nervousness

3. Shock-like sensation at the initiation of tDCS

Changes in the activity of the prefrontal region have the potential to induce acute changes in mood. Hypomania has been reported in a few patients receiving tDCS for bipolar disorder[22,23] and depression[24] but not, to our knowledge, in patients not suffering from mood disorders. To minimize risk of exacerbating a comorbid mental health condition, individuals with moderate to severe symptoms of a poorly controlled comorbid condition will be excluded.

It is important to note that many of the side effects listed above have been also reported in association with sham tDCS, even with similar rates[21].

Although there are no reports suggesting increased risk for tDCS during pregnancy, pregnant women are excluded from this study due to insufficient knowledge of the effects of the strong magnetic fields on the fetus. Potential subjects who are female and of childbearing age will be asked about their pregnancy status, sexual activity, whether pregnancy is being sought, and use of contraception. Study staff will record her responses to these questions. If the potential subject cannot rule out the possibility of pregnancy, or if her answers to these questions suggest pregnancy is possible, a pregnancy test will be conducted prior to study enrollment.

Risk from cognitive testing

Performing a task that measure executive functioning (e.g., Eriksen Flanker Task), as with any cognitive testing, can result in frustration related to difficulty with performance, or boredom during longer sittings. Participants may stop their participation at any time or refuse to answer questions that make them uncomfortable.

8. Benefits

It is potentially possible for subjects in the active tDCS group to experience an improvement in executive functioning after a single tDCS session, but this effect will likely be transient, dissipating after approximately 60 minutes. This is part of the known effects of tDCS and is a major reason why tDCS is used widely in basic human neuroscience studies with healthy controls. However, over the course of several weeks, subjects may experience a more permanent improvement in PASC cognitive deficits, specifically in the areas of processing speed and inhibitory control. Additionally, information gained in this study could reveal benefits in the PASC population that could then inform future treatment-oriented clinical trials.

9. Statistical Analysis

The effect of the tDCS on reaction time will be tested using a generalized linear mixed model (GLMM) with a Gamma distribution, whereas its effect on accuracy (percentage of correct responses) will be tested using a generalized logistic regression with mixed effects and a binomial distribution[25,26].

The mean amplitude of the ERPs will be modeled using a linear model with mixed effects and a normal distribution. The statistical analysis will focus on the significance of the interaction between the factors *StimType* (Active tDCS, Sham) and *TimePoint* (Baseline, Week 1, Week 4, Week 8). Subject ID will be added as a random-effect factor to account for baseline differences between the subjects.

Finally, the individual variables that may influence the response to tDCS (age, sex, education, and time from illness onset) will also be added to each model as covariates. For significant *StimType* x *TimePoint* interactions, pairwise post-hoc tests (e.g., Week 4>Baseline) will be conducted to determine the significance of these comparisons ($p<0.05$).

10. Monitoring and Quality Assurance

The principal investigators will oversee the collection, maintenance, and analysis of all data. He will also be responsible for ensuring that all adverse events are reported according to the Partners Human Research Committee Adverse Event Reporting Guidelines (http://healthcare.partners.org/phsirb/adverse.htm).

Any adverse events experienced by a subject will be communicated to a principal investigator and conveyed to the IRB. The principal investigators will review the completeness and accuracy of informed consent after each patient. The performance data will be automatically recorded on the computer workstation to ensure accuracy. Access to this digital data will require a password.

Every effort will be made to maintain patient confidentiality. We will use a coded ID numbers consisting of sequential numbers and a combination of letters on all results acquired and stored. The only name identification can be found on the consent form and other forms the subject has filled out. Partners consent forms will be stored in a designated locked cabinet. No identifying information will be used in any publications or presentations that emerge from this data.

Any experimental data will be passed on only to the principal investigators, co-investigators, and to study staff. Information derived from this study will be made available to the IRB. The information collected in our study will be used only for research purposes. Computer-based data and hardcopies will be made available only to the research team, e.g. stored on password-protected computers or in locked file cabinets. We will use only the minimum amount of information necessary for our study. Data will not be part of a patient's chart, as this information is investigational only, and not diagnostic. All researchers are trained in methods to protect confidentiality.

All adverse events and unanticipated problems involving risks to subjects or others will be reported to the HRC in accordance with HRC adverse event and unanticipated problems reporting guidelines.

11. Privacy and Confidentiality

- ☒ Study procedures will be conducted in a private setting
- ☒ Only data and/or specimens necessary for the conduct of the study will be collected
- ☒ Data collected (paper and/or electronic) will be maintained in a secure location with appropriate protections such as password protection, encryption, physical security measures (locked files/areas)
- ☐ Specimens collected will be maintained in a secure location with appropriate protections (e.g. locked storage spaces, laboratory areas)
- ☒ Data and specimens will only be shared with individuals who are members of the IRB-approved research team or approved for sharing as described in this IRB protocol
- ☐ Data and/or specimens requiring transportation from one location or electronic space to another will be transported only in a secure manner (e.g. encrypted files, password protection, using chain-of-custody procedures, etc.)

- ☒ All electronic communication with participants will comply with Mass General Brigham secure communication policies
- ☒ Identifiers will be coded or removed as soon as feasible and access to files linking identifiers with coded data or specimens will be limited to the minimal necessary members of the research team required to conduct the research
- ☒ All staff are trained on and will follow the Mass General Brigham policies and procedures for maintaining appropriate confidentiality of research data and specimens
- ☒ The PI will ensure that all staff implement and follow any Research Information Service Office (RISO) requirements for this research
- ☒ Additional privacy and/or confidentiality protections

A secure web-based video chat program will be used to conduct the remotely supervised home tDCS sessions.

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APPENDIX A

Data Monitoring Committee / Data and Safety Monitoring Board Appendix

- *To be completed for studies monitored by Data Monitoring Committee (DMC) or Data and Safety Monitoring Board (DSMB) if a full DMC/DSMB charter is not available at the time of initial IRB review.*
- *DMC/DSMB Charter and/or Roster can be submitted to the IRB later via Amendment, though these are not required.*

A Data Monitoring Committee (DMC) or Data and Safety Monitoring Board (DSMB) will be convened for safety monitoring of this research study. The following characteristics describe the DMC/DSMB convened for this study (Check all that apply):

- ☐ The DMC/DSMB is independent from the study team and study sponsor.
- ☐ A process has been implemented to ensure absence of conflicts of interest by DMC/DSMB members.
- ☐ The DMC/DSMB has the authority to intervene on study progress in the event of safety concerns, e.g., to suspend or terminate a study if new safety concerns have been identified or need to be investigated.
- ☐ Describe number and types of (i.e., qualifications of) members:
  Click or tap here to enter text.
- ☐ Describe planned frequency of meetings:
  Click or tap here to enter text.
- ☐ DMC/DSMB reports with no findings (i.e., “continue without modifications”) will be submitted to the IRB at the time of Continuing Review.
- ☐ DMC/DSMB reports with findings/modifications required will be submitted promptly (within 5 business days/7 calendar days of becoming aware) to the IRB as an Other Event.