Title: Home-based tDCS in Major Depressive Disorder (MoodStim)

NCT04799405

01/13/2021

Title: Home-based Transcranial direct current stimulation (tDCS) in Major Depressive Disorders
IRB #: HSL # 2020-3, Advarra Protocol # PRO00044198
Creation Date: 4-10-2020, version 2 01132021

Principal Investigator: Alvaro Pascual-Leone
Marcus Institute for Aging Research
Address: 1200 Centre Street, Boston, MA 02131-1101
Phone: 617-971-5372
Email: apleone@hsl.harvard.edu

Co-Investigators:

Name: Bradley Manor
Organization: Marcus Institute for Aging Research
Address: 1200 Centre Street, Boston, MA 02131-1101
Phone: 617-971-5339
Email: BradManor@hsl.harvard.edu

Name: Lewis Lipsitz
Organization: Marcus Institute for Aging Research
Address: 1200 Centre Street, Boston, MA 02131-1101
Phone: 617-971-5318
Email: Lipsitz@hsl.harvard.edu

Name: Eran Metzger
Organization: Hebrew SeniorLife
HealthCare Services and HRC
Email: metzger@hsl.harvard.edu

Purpose of the study

Major depressive disorder (MDD) is highly prevalent and the main cause of global disability worldwide (Kupfer et al., 2012). About 20–40% of patients do not benefit sufficiently from the existing antidepressant interventions, including trials of medication and psychotherapy (Greden, 2001). Pharmacological treatments have limited efficacy, side effects are common (Carvalho et al., 2016), and one-third of patients are medication-resistant failing to achieve remission after using three or more antidepressants (Rush et al., 2006) and experiencing recurrent depressive episodes (Nemeroff, 2007).

For patients with medication-resistant MDD, a number of neuromodulation strategies are available, including electro-convulsive therapy (ECT) and repetitive transcranial magnetic stimulation (rTMS). These are effective interventions, which nonetheless present relatively high costs, may have side-effects and risks (e.g. complications of anesthesia in the case of ECT or risk of seizure induction in the case of rTMS), and require specialized equipment, trained personnel and suitable clinic facilities. This can pose a challenge for some patients as ready access to specialized clinics or treatment centers is not available in all areas of the US or worldwide. The challenge is particularly acute among seniors who have additional limitations in mobility and need help and support to make it to outpatient clinics. And yet, it is estimated that approximately 15% of the elderly (aged > 65) living in the community suffer from clinically significant depressive symptoms (Blazer 2003). Depression in the elderly is a cause of particularly high morbidity and early mortality (Schulz et al. 2002), and older age is a significant predictor of an unfavorable course of depression (Mitchell & Subramanian 2005), reduced likelihood of treatment response (Licht-Strunck et al 2007; Tedeschini et al. 2011), diminished chance of functional recovery (Little et al 1998), and increased risk of relapse (Beekman et al 2002).

At present, given the COVID-19 pandemic and the required and appropriate restrictions on individual mobility and outpatient medical encounters and procedures, access to rTMS, ECT, or similar in-clinic treatments is much more limited. These added difficulties to access ECT and rTMS are occurring at a time when the risk of mental health problems and of decompensation from pre-existing depression is extremely high due to the uncertainties, fears, and stressors caused by the COVID-19 pandemic and the social distancing. The risk of mood and mental health decompensation in the setting of social isolation and loneliness is particularly high among the elderly, who in turn are at a particularly high risk of serious complications of an infection with COVID-19 and thus are faced with particularly high stress, fears, and strict isolation regulations.

Therefore, the current COVID-19 pandemic makes the need for a safe, effective, home-based intervention for an acute, medication-resistant episode of uni- or bi-polar MDD particularly urgent. Transcranial direct current stimulation (tDCS) offers a suitable and readily available solution.

Study design and purpose: We propose a safety/feasibility study designed to determine whether it is possible for transcranial direct current stimulation (tDCS) interventions to be successfully delivered by a caregiver at the homes of adults who have medication-resistant MDD.

Study objectives:

Primary objective: Demonstrate that remote tDCS sessions applied by a caregiver are feasible, complied and adhered to, and are safe in individuals with severe depression

Secondary objective: Gather pilot data on the potential of home-based tDCS to induce clinically meaningful improvements in the severity of depression in individuals who would otherwise be offered rTMS or ECT treatment.

The ultimate goal of this work is to prepare the path for a subsequent randomized clinical trial to assess the antidepressant therapeutic efficacy of home-based tDCS. We thus propose a study of tele-health supervised, caregiver-delivered, home-based tDCS for antidepressant treatment of patients with a medication-resistant depression episode of uni- or bi-polar Major Depression who would otherwise qualify for rTMS or ECT.

Specifically, in the present protocol we seek to offer participation to:

- Patients with medication-resistant MDD who have undergone rTMS or ECT and responded to it but whose benefit has lapsed, and they need repeat a rTMS or ECT course that they cannot access
- Patients with medication-resistant MDD who are undergoing rTMS or ECT and responding, but cannot continue to get the rTMS or ECT course due to COVID-19 pandemic-related regulations or other access concerns
- Patients with medication-resistant MDD who are referred to rTMS or ECT and are found well qualified but cannot access rTMS or ECT due to COVID-19 pandemic-related regulations or other access concerns.

The benefits of this project address a present need due to the COVID-19 pandemic, but also go beyond the present situation and address a larger, pre-existing need.

Across all these potential groups of participants, prospective participants will:

1. Need to have a primary psychiatrist who agrees to their participation in the study and is willing to continue to follow the patient and work collaboratively with the study team
2. Need to be assessed by their primary psychiatrist to be stable enough to be able to remain at home and participate in the present study without undue risk to their safety
3. Need to be living with an adult willing and capable to provide oversight and learn to deliver the home-based tDCS
4. Have the capability to connect with the study team for daily supervision of the intervention sessions and close safety monitoring, and be willing to commit to doing so

Background

Transcranial direct current stimulation (tDCS) tDCS is a painless method for focal brain stimulation. tDCS is based on decades-old observations that neuronal firing is modulated by low amplitude electrical direct current (DC). Specifically, when applied to the cerebral cortex, cathodal DC inhibits neuronal firing (Creutzfedt, 1962, Nitsche, 2000). The mechanisms by which cathodal DC reduces neuronal firing likely relate to hyper-polarization of the soma membrane which occurs when the apical dendrites neurons are oriented toward the cathode in a constant electric field. The practical application of tDCS is simple: low amplitude DC is administered via scalp electrodes such that the cerebral cortex is exposed to cathodal DC beneath one of the electrodes, and the return (anodal) electrodes can be placed anywhere else on the body, or in more complex arrangements to minimize currents at any site. tDCS methods have also recently been adapted to rats for work with disease models (Kabakov 2012, Rotenberg, 2014). Hundreds of tDCS trials have demonstrated the technique to be well tolerated and safe. Direct electrical current stimulation is presently FDA-approved for extracranial use, and FDA applications for cranial stimulation (tDCS) for management of mood disorder and chronic pain are in progress. tDCS units are also inexpensive and lightweight. The electrical supply can be derived from conventional 9-volt batteries. The scalp electrodes can be fastened in seconds. tDCS can be combined easily with other therapies, such as those that may be required for resuscitation of an acutely injured patient. tDCS is presently under investigation as a treatment for epilepsy (IDE attached to this one), where excess cortical excitability is a prominent feature of the disease

process, and where neuronal inhibition may be beneficial. The tDCS stimulator used in this clinical study is the STARSTIM device (Neuroelectrics, Inc). Starstim has an associated software that allows to personalize treatment per pathology and target different brain region.

tDCS and Depression

Transcranial direct current stimulation (tDCS) delivers weak currents into the brain through two or more electrodes placed on the scalp. When appropriate guidelines are followed, tDCS is safe and extremely well tolerated (Antal et al., 2017). The mechanisms of action remain insufficiently understood but appear to involve polarity-dependent shifts in neuronal membrane potentials, thus leading to purely neuromodulatory effects that modify likelihood of neuroplasticity effects (potentiating or suppression plasticity depending on anodal versus cathodal effects). Notably tDCS effects spread across functional brain networks and thus enable modulation of brain connectivity related to mood disorders and MDD.

There has been a fairly large number of studies, including randomized, sham-controlled clinical trials (RCTs) on the effects of tDCS in MDD. Results have been variable and in part discrepant. For example, Brunoni et al., (2017) found tDCS to have similar efficacy to antidepressant medications, while Loo et al., (2018) found no efficacy of real tDCS over sham in MDD. Nonetheless, several meta-analyses have concluded that tDCS is effective for MDD (Mutz et al., 2018; Brunoni et al., 2016). Most recently, Razza et al. (2020) completed a systematic review of all studies of tDCS for treatment of acute major depressive episodes completed up to January 2020. They included all randomized, sham-controlled clinical trials (RCTs) enrolling participants with an acute depressive episode, a total of 23 RCTs with 1,092 participants. They found that active tDCS was superior to sham regarding endpoint depression scores, response and remission rates. Moreover, active tDCS was safe with a side-effect profile comparable to sham. Moffa et al. (2020) also recently published an individual patient data (IPD) meta-analysis evaluating the efficacy and acceptability of tDCS for treatment of acute major depressive episodes. The IPD meta-analysis is more accurate in estimating the efficacy of an intervention and also superior to the aggregated data approach for obtaining predictors of treatment outcome since it uses the raw data of each participant collected from each study (Riley et al., 2010). Moffa et al. included data from all published placebo-controlled trials on tDCS as only intervention in MDD conducted until December-2018. This included 9 eligible studies with a total of 572 participants. They found active tDCS to be significantly superior to sham for an antidepressant response (30.9% vs. 18.9% respectively; OR = 1.96), remission (19.9% vs. 11.7%, OR = 1.94), and depression improvement (effect size $\beta = 0.31$). Moreover, they found a consistent continuous clinical improvement after the end of the tDCS treatment course. It is noteworthy that the clinical efficacy was substantially higher in the studies where the tDCS course was longer (3-4 weeks versus 1-2 weeks).

The variability in the literature on the antidepressant effects of tDCS may reflect differences in patient selection as well as in the tDCS protocol. Longer courses of treatment seem particularly important to ensure sustained, lasting benefits. Consistent with current understanding of mechanisms of action, tDCS antidepressant effects may involve long-term neuroplastic changes that take time to develop and may in fact continue to evolve and mature even after the tDCS treatment course has ended. This makes long treatment courses with maintenance phases important, and home-based interventions appealing. Importantly, across all studies, active tDCS has been well tolerated and there have been no significant adverse or side effects.

Home Use of tDCS

tDCS, as a relatively simple and portable technology, is particularly well suited for remotely-supervised, home-based treatment, which would facilitate longer periods of treatment as well as offer a suitable therapeutic option at the present time as we aim to deal with the COVID-19 pandemic.

Several equipment manufacturers have developed tDCS systems for remotely-supervised, home-based use, where the treatment is administered by the patient or a caregiver.

Treatment parameters, scheduling and outcomes can be monitored remotely by clinic or research staff. To date, this has been piloted for treatment of a number of conditions including neuropathic pain (Garcia-Lorrea et al., 2019), auditory hallucinations in schizophrenia (Andrade, 2013), multiple sclerosis (Charvet et al., 2017; Charvet et al., 2018; Kasschau et al., 2016; Kasschau et al., 2015), Mal de Debarquement Syndrome (Cha et al., 2016), Parkinson's disease (Agarwal et al., 2018; Dobbs et al., 2018), trigeminal neuralgia (Hagenacker et al., 2014), vascular dementia (André et al., 2016) and Prader-Willi syndrome (Azevedo et al., 2017) with promising results.

Palm et al. (2018) completed a systematic review of all available evidence on home use of tDCS until May 2017. They identified 22 original research papers, trial protocols or trial registrations involving home-use tDCS, mostly as an add-on intervention to cognitive or physiotherapeutic intervention. Study samples were small, and many were single-blinded studies focused on feasibility and safety. Nonetheless, Palm et al. were able to show that treatment adherence was high and side-effects minimal, and thus they concluded that remotely controlled and supervised home-used tDCS was feasible and promising. The experience with home-use tDCS has continued to grow since then.

In the setting of depression, Clayton et al., (2018) reported a case of one patient with comorbid multiple sclerosis and recurrent depressive episodes who received a course of remotely supervised tDCS following ECT treatment. Fatigue and mood ratings improved. More recently, Alonzo et al. (2019) completed a proof-of-principle, open-label trial in 34 participants who were taught to self-administer 20–28 tDCS sessions (2 mA, 30 min, F3-anode and F8-cathode montage according to 10–20 EEG placement) over 4 weeks followed by a taper phase of 4 sessions 1 week apart. Participants were initially monitored via video link for a few days, and then through completion of an online treatment diary. Participants met criteria for a diagnosis of MDD according to the DSM-IV-TR, as determined via an interview with a study psychiatrist, and confirmed with the Mini International Neuropsychiatric Interview (MINI; Version 5.0.0) (Sheehan et al., 1998). Inclusion criteria included a current major depressive episode of at least four weeks duration as part of a uni- or bipolar depression; and a score of at least 20 on the Montgomery–Asberg Depression Rating Scale (MADRS) at trial entry. Exclusion criteria were any DSM-IV-TR psychotic disorder; drug or alcohol abuse or dependence in the preceding 3 months; concurrent benzodiazepine medication; high suicide risk; history of clinically defined neurological disorder or insult; metal in the cranium or skull defects; skin lesions on the scalp at the proposed electrode sites; and pregnancy. Participants on antidepressant medication were permitted to enter the trial provided the medication dose was unchanged for 4 weeks prior to trial entry and during the acute treatment phase of the study. One participant was withdrawn from the study due to too many missed sessions. The remaining 33 participants completed 93% of the scheduled sessions in the initial 4-week phase. Ten of thirteen participants (77%) who qualified for the maintenance phase opted to continue. Mood improved significantly from baseline (27.5 on MADRS) to 1 month after the end of acute treatment (MADRS 15.5; $p < 0.001$). Side effects reported across a total of 1,149 sessions were minimal, primarily mild to moderate tingling or burning/heat sensation during stimulation and redness at the electrode sites. This study provides clear, initial evidence that home-based, remotely supervised tDCS treatment is feasible for depressed patients and offers a potentially effective intervention.

Process of Consent

Potentially eligible individuals (Participants with MDD and their participant caregiver-administrators) will each be emailed or snail-mailed (per request, and according to their preference) a copy of the informed consent for them to review at their own pace prior to the telephone screening call. Written or verbal informed consent will be obtained by study personnel at the beginning of this in-person screening call, depending on the ability of the research team to have personal contact due to the restrictions imposed by COVID-19 precautions.

Home-use device and training to caregivers

Alonzo et al. (2019) used a tDCS device that required the placement of individual, large sponge electrodes onto the scalp in positions defined by the 10-20 EEG electrode placements (F3 and F8) The large sponge electrodes needed to be held in place by elastic bands. The procedure posed substantial challenges and precluded some caregivers from achieving appropriate level of competency. In addition, the interface with a programmable device for specification of stimulation parameters was challenging and again represented a hurdle for some patient-caregiver pairs.

Neuroelectrics has developed a system for home-based tDCS that effectively overcomes these challenges and is being used in several studies, e.g. Garcia-Lorrea 2019 https://clinicaltrials.gov/ct2/show/NCT02346396). The Starstim Home Kit® (Neuroelectrics Corp) is commercially available and approved in Canada for use in treating chronic pain, depression and addictive disorders. It utilizes the company's industry leading Starstim system, with additional features that enable researchers and clinicians to "prescribe" and monitor home-based tDCS to end users. Briefly, the Starstim system resembles a swimming cap that fits loosely on the head, but with small electrodes that lie on the scalp and deliver low-level electrical currents to targeted brain regions. Within the Home Kit, the relevant electrode positions are marked on the headcap with different colors and numbers, and the corresponding electrode leads (cables) from the tDCS device are marked with the same colors and numbers. This ensures that the user places the electrodes in the correct position and secures the correct lead to each electrode. The Home Kit also utilizes a tablet that provides the user with step-by-step instructions to set up the Starstim device, check electrode impedance, and record side effects. The user may also videoconference with remote staff in real-time. The researcher uses Neuroelectrics online Portal (NE Portal) to remotely schedule sessions and monitor in real-time specific treatment events to ensure safety.

At the Marcus Institute we have developed a training and in-home supervision program to accompany the Starstim Home Kit and have established its feasibility in two ongoing studies (one focused on gait and balance and the other on episodic memory in dementia). In these studies, to date we have completed the assessments of eight participant 'pairs;' that is, an individual to receive tDCS along with a family member, friend, or care-giver willing and able to administer tDCS. Each potential administrator was initially screened to ensure that they would be available throughout the intervention period and to ensure they had at least minimal computer proficiency. They were then trained by staff to administer tDCS to the study participant and did so under the supervision of staff until they self-reported comfort in the process and were deemed proficient as determined with a custom-developed checklist. For all eight participant-pairs, the administrators, who ranged in age from 44 to 87, achieved proficiency by the third session of tDCS. All but one pair completed at least eight sessions of the 10-session intervention. No adverse events were reported. Transient skin redness and tingling sensations under the electrode were the only reported side effects and the frequency and severity of these side effects were similar to that reported in published staff-administered interventions. Upon exit interview, all administrators—and the participants who received the stimulation—stated that the Home Kit and training materials were easy to use, that

they were satisfied with the experience and training they received, and that they would be willing to use to system again in the future.

The above studies utilize in-person training methods until the participant administrator achieves proficiency. For the current proposal, a video telemedicine-based training program is available to ensure minimal staff-participant contact. Moreover, a pre-configured Starstim system will be shipped directly to the participants with all the required supplies and documentation.

Eligibility Criteria: Patients meeting one of the following criteria may be eligible to participate in this study.

1. Patients with medication-resistant MDD who have undergone rTMS or ECT and responded to it but whose benefit has lapsed, and they need repeat a rTMS or ECT course that they cannot access

2. Patients with medication-resistant MDD who have undergone rTMS or ECT and responded to it but whose benefit has lapsed, and they need repeat a rTMS or ECT course that they cannot access

3. Patients with medication-resistant MDD who are undergoing rTMS or ECT and responding, but cannot continue to get the rTMS or ECT course due to COVID-19 pandemic-related regulations or other access concerns

4. Patients with medication-resistant MDD who are referred to rTMS or ECT and are found well qualified but cannot access rTMS or ECT due to COVID-19 pandemic-related regulations or other access concerns.

The benefits of this project address a present need due to the COVID-19 pandemic, but also go beyond the present situation and address a larger, pre-existing need. Across all these potential groups of participants, prospective participants will:

- need to have a primary psychiatrist who agrees to their participation in the study and is willing to continue to follow the patient and work collaboratively with the study team

- need to be assessed by their primary psychiatrist to be stable enough to be able to remain at home and participate in the present study without undue risk to their safety

- need to be living with an adult willing and capable to provide oversight and learn to deliver the home-based tDCS

- have the capability to connect with the study team for daily supervision of the intervention sessions and close safety monitoring, and be willing to commit to doing so

Inclusion criteria - Individuals with MDD

Participants will be men and women who:

- Are aged 50 or older
- Able to read, write, and communicate in English
- Have a caregiver who is willing and able to provide the home tDCS sessions.
- Participants must be under the care of a treating psychiatrist who approves of the study participation and believes that TMS or ECT is indicated for his/her patient but that
    - it would not endanger the patient to participate in the present study rather than pursue such alternative, or
    - the patient could not gain access to TMS or ECT due to COVID-19

(*The depression phase of bi-polar disorder is not a reason for exclusion if the treating psychiatrist believes TMS or ECT would be indicated*).

Participants with MDD must fit into one of the following 3 groups (***medication-resistant MDD defined as 1) participant's condition has not responded to prescribed antidepressant medication; 2) participant is medication intolerant, or 3) some other underlying reason):***

- Patients with medication-resistant Major depressive disorder (MDD) who have undergone repetitive transcranial magnetic stimulation (rTMS) or electroconvulsive therapy (ECT) and responded to it but whose benefit has lapsed and they need repeat rTMS or ECT course that they cannot access;
- Patients with medication-resistant MDD who are undergoing rTMS or ECT and responding, but cannot continue to get the rTMS or ECT course due to COVID-19 pandemic-related regulations or other access concerns
- Patients with medication-resistant MDD who are referred to rTMS or ECT and are found well qualified but cannot access rTMS or ECT due to COVID-19 pandemic-related regulations or other access concerns.

Further, participants must:

- Meet criteria for a diagnosis of MDD according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) (American Psychiatric Association, 2000), as determined via an tele-health interview with a study psychiatrist, and confirmed with the Mini International Neuropsychiatric Interview (MINI; Version 5.0.0) (Sheehan et al., 1998) and the prospective participant's primary psychiatrist.
- Currently experiencing a major depressive episode of at least four weeks' duration as part of a unipolar or bipolar depression. Score will need to be at least 20 on the MADRS.

Participant caregiver-administrators:

Caregiver-administrators will be men and women, who may be a spouse, family member or friend who is

- At least 21 years of age
- Able to read, write, and communicate in English
- Self-reported computer proficiency and willingness to learn how to use tDCS as defined by "yes" answers to the questions "Do you feel comfortable using a computer?" and "are you willing to learn
- How to administer tDCS?" Stated availability throughout the study period to administer tDCS sessions to

the participant with MDD.

Exclusion criteria for participants with MDD will be:

- Any DSM-psychotic disorder
- Drug or alcohol abuse or dependence in the preceding three months;
- Concurrent benzodiazepine medication;
- High suicide risk (*Utilizing the Beck Depression Inventory and the Hamilton Depression Scale, suicide risk will be assessed at baseline by the study psychiatrist*) ;
- History of clinically defined neurological disorder or insult; Metal in the cranium or skull defects;
- Skin lesions on the scalp at the proposed electrode sites;
- Pregnancy.
- Medical devices (i.e. cardiac pacemaker, deep brain stimulator, medication infusion pump, cochlear implant, vagus nerve stimulator).
- Previous skull surgery with resultant skull defects
- Inability to understand study procedures following review of the Informed Consent form.

  Understanding will be assessed by asking the participant with MDD to answer the following three questions:
  1) What is the purpose of this study?

  2) What are the risks of study involvement?

  3) If you decide to participate, are you allowed to withdraw from the study at any time?

  Answers will be recorded by study personnel on the "Assessment of Protocol Understanding" form. Insufficient understanding will be defined by one or more incorrect answers, as determined at the discretion of the investigator.

Exclusion criteria for Participant caregiver-administrators:

- Poor eyesight,
- Severe arthritis in the hands, pain, deformity or other condition that interferes with successful administration of tDCS.
- Inability to understand study procedures following review of the Informed Consent form.

  Understanding will be assessed by asking the participant caregiver-administrator to answer the following three questions:

  1) What is the purpose of this study?

  2) What are the risks of study involvement?

  3) If you decide to participate, are you allowed to withdraw from the study at any time?

  Answers will be recorded by study personnel on the "Assessment of Protocol Understanding" form (see attached). Insufficient understanding will be defined by one or more incorrect answers, as determined at the discretion of the investigator

Adverse Events

An adverse event is any untoward medical occurrence in a participant, whether or not is is causally related to the study. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the study.

Adverse events will be recorded on the appropriate case report forms and source documents. The investigator and/or trained staff member will evaluate all adverse events as to their severity and relation to the test article. The severity of adverse events will be graded as follows:

Mild: Awareness of a sign or symptom but easily tolerated.

Moderate: Discomfort sufficient to cause interference with usual activity or to affect clinical status.

Severe: Incapacitating with inability to do usual activity or to significantly affect clinical status.

Life Threatening: The participant was at immediate risk of death from the adverse event as it occurred.

The Investigator will also assess the relationship of any adverse event to study, based upon available information, using the following guidelines:

0 = Unlikely: No temporal association, or the cause of the event has been identified. 1 = Possible: Temporal association, but other etiologies are likely to be the cause; however, involvement of the study procedures cannot be excluded.

2 = Probable: Temporal association, other etiologies are possible, but not likely.

A *serious adverse event* is any experience that results in any of the following outcomes: death,is life threatening, results in inpatient hospitalization or prolongation of hospitalization, a persistent or significant disability/incapacity.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Side effects associated with tDCS according to the most recent data available (Brunoni, Fregni, & Pagano, 2011; Nitsche et al., 2008; Antal et al, 2007; Moliadze, Antal, & Paulus, 2010; Brignani, Ruzzoli, Mauri, & Miniussi, 2013) are:

Sensations reported by subjects under the electrodes: (These sensations can sometimes continue throughout and for a brief period following completion of the tDCS but usually resolve shortly after the initiation of tDCS)

Mild tingling (20-70%

Light itching (30-40%)

Slight burning (10-22%) Discomfort or mild pain (10-18%)

Other effects that can occur both during and after tDCS include: Skin redness (20%)

Mild fatigue (15%)

Headache (10-15%)

Difficulties in concentration (11%)

Additionally the following rare side effects have been described: Nausea (<1%)

Nervousness (<1%)

Although it has never been reported in tDCS, seizures are a theoretical risk. Individuals with a history of seizures and/or a diagnosis of epilepsy will therefore be excluded from this study. EEG has not associated adverse events and is considered safe and painless.

All adverse events, Serious Adverse Events and Unanticipated Problems will be reported to the Advarra IRB according to its policies.

References:

Antal, A., Brepohl, N., Poreisz, C., Boros, K., Csifcsák, G. & Paulus, W. Transcranial direct current stimulation over somatosensory cortex decreases experimentally induced acute pain perception. Clin J Pain 2008; 24(1):56-63. http://doi.org/10.1097/AJP.0b013e318157233b Brignani, D., Ruzzoli, M., Mauri, P., & Miniussi, C. (2013). Is transcranial alternating current stimulation effective in modulating brain oscillations? PloS One, 8(2), e56589. http://doi.org/10.1371/journal.pone.0056589 Brunoni, A. R., Fregni, F., & Pagano, R. L. (2011). Translational research in transcranial direct current stimulation (tDCS): a systematic review of studies in animals. Reviews in the Neurosciences, 22(4), 471â481. http://doi.org/10.1515/RNS.2011.042 Moliadze, V., Antal, A., & Paulus, W. (2010). Boosting brain excitability by transcranial high frequency stimulation in the ripple range. The Journal of Physiology, 588(Pt 24), 4891â4904. http://doi.org/10.1113/jphysiol.2010.196998 Nitsche, M. A., Cohen, L. G., Wassermann, E. M., Priori, A., Lang, N., Antal, A., & Pascual-Leone, A. (2008). Transcranial direct current stimulation: State of the art 2008. Brain

Stimulation, 1(3), 206â223. http://doi.org/10.1016/j.brs.2008.06.004

Risks

The medical risks are described in the adverse event section. Other risks related to the loss of confidentiality are described in the confidentiality section with steps we will take to mitigate any such risk.

Participant Burden: Participation in this protocol will require moderate subject time and effort. Therefore, in addition to recommended safety measures described below, additional efforts will be taken to minimize subject burden and maximize retention throughout the study. It is of note that our study team has a strong track record of successful clinical research requiring similar participation and retention has been high in these efforts.

Several strategies will be employed to minimize subject burden and maximize adherence to the protocol.

Specifically we will:

- Develop a personal relationship between subjects and members of the staff by matching research assistants with individual participants.
- Schedule appointments at convenient times with familiar staff.
- Explain to subjects all aspects of their participation.

- Provide reminders of all appointments.
- Include personal notes in the subject's data file to remember events in the life of the participant; these can be commented on at future visits (e.g. birth of a grandchild)

Any participant who suffers an adverse event during the conduct of study protocols will be triaged immediately by the medical investigators, and the study psychiatrist. The study PI and study psychiatrist will monitor and manage all study related A/E's. If follow up care is needed to treat an A/E, the investigators will arrange to have this care provided at a nearby institution, convenient to the study participant. . The treating provider will bill the insurance company or other third parties, if appropriate, for the care a participant receives for any injury. We will try to have these costs paid for, but the participant may be responsible for some of them. For example, they may be responsible for payment of any deductibles and co-payments required by the insurer. There are no plans to provide any compensation for an injury beyond what is described above, should one occur.

If there is a change in the clinical condition of the participant, the study psychiatrist will contact the subject's treating/primary psychiatrist so that appropriate primary clinical care can be provided.

If, during the course of this study, the participant experiences an urgent medical need, he/she will be advised to seek immediate medical care, including contacting their primary care physician/psychiatrist as indicated.

There is no cost to the participant or insurer for the device.

Benefits

While there are no definitive benefits to participants as a result of participation in this study, MDD participants who received tDCS interventions in prior studies showed improvement of symptoms.

Most recently, Razza et al. (2020) completed a systematic review of all studies of tDCS for treatment of acute major depressive episodes completed up to January 2020. They included all randomized, sham-controlled clinical trials (RCTs) enrolling participants with an acute depressive episode, a total of 23 RCTs with 1,092 participants. They found that active tDCS was superior to sham regarding endpoint depression scores, response and remission rates. Moreover, active tDCS was safe with a side-effect profile comparable to sham.

Moffa et al. (2020) also recently published an individual patient data (IPD) meta-analysis evaluating the efficacy and acceptability of tDCS for treatment of acute major depressive episodes. The IPD meta-analysis is more accurate in estimating the efficacy of an intervention and also superior to the aggregated data approach for obtaining predictors of treatment outcome since it uses the raw data of each participant collected from each study (Riley et al., 2010). Moffa et al. included data from all published placebo-controlled trials on tDCS as only intervention in MDD conducted until December-2018. This included 9 eligible studies with a total of 572 participants. They found active tDCS to be significantly superior to sham for an antidepressant response (30.9% vs. 18.9% respectively; OR = 1.96), remission (19.9% vs. 11.7%, OR = 1.94), and depression improvement (effect size $\beta = 0.31$). Moreover, they found a consistent continuous clinical improvement after the end of the tDCS treatment course. It is noteworthy that the clinical efficacy was substantially higher in the studies where the tDCS course was longer (3-4 weeks versus 1-2 weeks).

The ultimate goal of this work is to identify the potential of tDCS as a home therapy to induce improvements of MDD for patients with the disease. We anticipate that this specific study will demonstrate that remote tDCS sessions are feasible in this population, and offer an important and convenient alternative for multi-session tDCS administration in adults with MDD.

Visits (All visits will be conducted remotely)

For this study, participant caregiver administrators will be provided remote step-by-step training to administer the tDCS sessions to the participants with MDD. Participant caregiver-administrators will be directly supervised remotely, until they demonstrate proficiency, without coaching by the study team. We have developed a step by step training manual, and have successfully trained older adult caregivers to administer the tDCS.

Visit	Purpose	Procedures	Study personnel	Duration	Location
Pre-ICF	Advance review	Informed consent pre-review by potential participants	RA will send	As needed for review	Mailed/emailed to P
Visit 1	Remote screen and assessment visit	Informed consent [***P with MDD]*** Mental Health/Medical health history; medications; Cognitive Assessment; Interview with study psychiatrist [***Participant caregiver-administrators***] Health history; computer proficiency questionnaire [***Both participants***] tDCS overview and training	Study research assistant; Study psychiatrist	~ 1 hour	Remote
Home tDCS administration Treatment period – Daily tDCS sessions over 4 weeks **Participant ratings of suicidality will be completed each day, and responses will be monitored and immediately be reviewed in real time by the study RA and study psychiatrist. Any changes from baseline will result in an immediate contact to the participant by the study psychiatrist.*					
Week (Wk)1; Day (D) 1	Home-based tDCS	At-home tDCS equipment set-up; tDCS administration by caregiver-administrator with step-by- step remote training by study staff Daily diary	Study research assistant	1 hour total (tDCS session=30 mins)	Video conference
Wk1, tDCS session	Home-based tDCS once a day	tDCS admin by the caregiver-administrator with remote staff oversight and coaching Daily	Study research assistant	1 hour total (tDCS session=30	Video conference

D 2-4		diary		mins)	
Wk 1, tDCS session D 5	Home-based tDCS	tDCS admin by the caregiver-administrator with remote staff oversight and coaching; Staff administered skills test for caregiver-administrators Daily diary	Study research assistant	1 hour total (tDCS session=30 mins)	Video conference
Wk 1-4; D6-28	Home-based tDCS once a day	The caregiver-administrator will administer the in-home tDCS session with remote staff monitoring and video conferencing if necessary Daily diary	Study research assistant	1 hour	Participant's Home
Wks 1-4, D 7, 14, 21, and 28	Weekly assessments	**Participants with MDD only** Week 1-4 Assessment completion (Day 7, 14,21, and 28); depression symptoms and quality of life assessments	Study research assistant	30 minutes	Phone
Home tDCS administration Treatment taper period – weeks 5-8 *Participant ratings of suicidality will be completed each day, and responses will be monitored and immediately be reviewed in real time by the study RA and study psychiatrist. Any changes from baseline will result in an immediate contact to the participant by the study psychiatrist.*					
Wk 5, D 30,32,34	Home-based tDCS Total of 3 sessions, one every other day over a 6 day period.	The caregiver-administrator will administer the in-home tDCS session with remote staff monitoring and video conferencing if necessary Daily diary	Study research assistant	1 hour	Participant's Home
Wk 6-7, D 37,40, 43	Home-based tDCS Total of 3 sessions, one every third day over a 9 day period	The caregiver-administrator will administer the in-home tDCS session with remote staff monitoring and video conferencing if necessary Daily diary	Study research assistant	1 hour	Participant's Home
Wk 8 D 47,51, 55	Home-based tDCS Total of 3 sessions, one every fourth day over a 12 day	The caregiver-administrator will administer the in-home tDCS session with remote staff monitoring and video conferencing if necessary Daily diary	Study research assistant	1 hour	Participant's Home

	period				
Wks 5-8 D35, 42, 49, 56	Weekly assessments	**Participants with MDD only** Weeks 5-8 Assessment completion (Day 35, 42,49, and 56); depression symptoms and quality of life assessments	Study research assistant	30 minutes	Phone
Home tDCS administration completed after Week 8, Day 55 session. Return of Home tDCS equipment to research team in the provided shipping materials and label.					
Four week follow-up period – weeks 9-12					
Wks 9-12 D57-84	Four week follow-up period	**Participants with MDD only** The study research assistant will maintain weekly contact with the participant over the 4 week follow-up period	Study research assistant	20 minutes	Phone
Week 12, Day 84	Final study assessment	**Both participants**: Final assessment completion, depression symptoms, quality of life assessments, cognitive assessment	Study research assistant	1 hour	Phone
End of study: Results sent to participant with MDD and treating psychiatrist					

Daily sessions (28 daily sessions): The device will be used to apply 20 minutes of tDCS to the participant with MDD's scalp in each of 28 daily sessions.

Thereafter, participants with MDD will undergo a taper phase of an additional 9 sessions of tDCS applied in progressively decreasing frequency until day #60 of the study as follows:

(1) First taper phase: three 30 minutes tDCS sessions applied every other day;

(2) Second taper phase: three 30 minutes tDCS sessions applied one every third day;

(3) Third and final taper phase: three final 30 minutes tDCS sessions applied one every fourth day.

The study team will predetermine, with the participant team, their most convenient two hour window for the home administration. During remote tDCS administration, the study team will be notified electronically by email when the tDCS session has been started and also when it has been completed, or if the tDCS session was aborted, or not completed during the predetermined two hour window.

The device will contain a sequence of simplified screen prompts for the participant,. To move to the next screen the participant will press a circle on the screen to continue (or to stop)

For example:

1. Hello
2. Battery status is GOOD
3. Today is Monday (date) It is now ( ) o'clock
4. Wear the Cap

5. Check the electrodes - 1 green is in the 1 green hole and secure, 2 yellow is in the 2 yellow hole and secure.
6. Are you ready for your 30 minutes session? If yes, press continue
7. Session has started, please stay in place until session is over [clock appears on screen to count down the minutes]
8. Session has ended, please stay in place while the device powers off.
9. Session is now completed! You may turn off the tablet, and remove the cap and electrodes

Daily sessions (28 daily sessions): The device will contain a block that will only allow one session to be administered within a 24 hour period. If a session is started and aborted, the participant will not be able to administer a new session until the next day, 24 hours later.

During the taper phase - the device block will only allow:

First taper phase: Three sessions, one every other day. If a session is started and aborted, the participant will not be able to administer a new session until 48 hours later. After the 3 sessions have been administered, (which will include any session that was started and aborted), a new session will not be available until the next scheduled session. The study team will monitor participant study adherence through completed sessions and through video conferencing and telephone contact.

Second taper phase: Three sessions, once every third day. If a session is started and aborted, the participant will not be able to administer a new session until 72 hours later. After the 3 sessions have been administered, (which will include any session that was started and aborted), a new session will not be available until the next scheduled session. The study team will continue to monitor participant study adherence through completed sessions and through video conferencing and telephone contact.

Third and final taper phase: Three sessions, once every fourth day. If a session is started and aborted, the participant will not be able to administer a new session until 96 hours later. After the 3 sessions have been administered, (which will include any session that was started and aborted), the sessions will be completed.

Statistical Methods and Analysis

Primary

Feasibility and tolerability/safety will be evaluated using home-based data as it is collected by reported number of aborted sessions.

The *primary outcome* will be change in the observer rated MADRS score from baseline to the 1-month follow-up.

Clinical response is defined as ≥ 50% improvement in MADRS score from baseline to the 1-month follow-up. Remission is defined as a MADRS score ≤ 10.

The *secondary outcome* measures will include the participant-rated Quick Inventory of Depressive Symptomatology (QIDS-SR) (Rush et al., 2003) and the Quality of Life Enjoyment and Satisfaction Questionnaire Short Form (Q-LES-Q-SF) (Endicott et al., 1993), both administered at the same time points as the MADRS. A computer-based cognitive test battery, CogState (https://www. cogstate.com), will provide an additional safety outcome measure. This battery includes tests designed to assess verbal learning and memory (International Shopping List Task), attention and psychomotor function (Detection Task), visual attention (Identification Task), visual learning and memory (One Card Learning Task), working memory (Two Back Task), and executive function (Set Shifting Task).

Statistics

Primary Analysis Plan for efficacy

The primary outcome measure is the median percentage change (across study subjects) in s MADRS from baseline to 1 month follow up. The significance of changes will be assessed using the non-parametric Wilcoxson signed-rank test; however, since this is a pilot study to determine effect sizes, demonstration of a significant effect is not a defined goal of the study.

Sample Size

The samples size of 50 is well within the sample size of previous published studies.

Withdrawal and Stopping the study

The criteria for discontinuing a participant's participation include the participant's request, as well as any unexpected life-threatening or potentially disabling event.

A study subject may be withdrawn from the study at any time if the study subject, the investigator, or the Sponsor feels that it is not in the study subject's best interest to continue.

All study subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

Reasonable attempts will be made by the investigator to provide a reason for study subject withdrawals. The reason for the study subject's withdrawal from the study will be specified in the study subject's source documents.

Stimulation Stopping criteria

Subject stimulation will be stopped if any of the following occur during the 8-week treatment period:

- Clinician impression of substantial worsening of medical condition
- If the study subject misses more than 10 stimulation visits.

Study subjects will be withdrawn from the study for the following:

- If the study subject is not compliant with the study procedures as determined by the investigator.
- If, in the investigator's opinion, it is not safe for the study subject to continue with participation in the study.
- If the study subject is withdrawn from the study, the subjects treating psychiatrist will be notified so that arrangements can be made for continued treatment of his/her MDD.
- The study team will be notified by email immediately if the subject reports any adverse events during any tDCS stimulation session, and immediate follow up will occur.
- Any adverse events that take place during testing will be reported to the PI (Dr. Alvaro Pascual-Leone)and recorded in the database. Drs. Pascual-Leone, Metzger and Lipsitz will have primary responsibility for monitoring participant safety in the trial. The investigators will be responsible for reviewing each adverse event in a timely fashion and preparing a summary report for submission to the IRB.

Data storage and confidentiality

Data will be kept on a secure, password protected HSL server in a REDCap Database. Only study members at the HSL site will have access to the HSL REDCap database. All hard copy forms will be kept in a locked filing cabinet that only study members will be able to access. All policies and procedures of Hebrew Senor LIfe with regard to data storage will be followed.

Data collected will be stripped of identifiers. Data will be assigned a code number and no personal identifying information will be associated with study data in any format, including electronically. Only the investigators will know information about a particular subject. Identifying information about a subject will be stored in locked computer files and cabinets and will not be used during the discussion, presentation, or publication of any research data.

Results of the study will be shared with the participant's psychiatrist if the participant has given study staff permission to do so.

List of Assessments and forms:

Sociodemographic form_2 8619.docx

Medical History Questionnaire_1 92718.docx

Medication Review Form_1 92818.docx

Q_LES_Q_SF.docx

QIDS_SR.pdf

Suicide Risk Assessment Protocol.pdf

tDCS Eligibility Questionnaire_41220.docx

001_Coverletter-Depression.docx

002_HOME_tDCS_MDD_STUDY_04_07_2020_v1.0.docx

003_Annex I- Safety Analysis of tDCS in Craniotomies.docx

004_Annex II-Home based tDCS for MDD Training Manual.docx

005_Annex III-Caregiver tDCS Competency Checklist.docx

006_Annex IV-SPR0157_lDLPFC_DepressionHome.pdf

Assessment of Understanding Protocol_mdd.docx

tDCS Side Effects Questionnaire_mdd.docx

FDA IDE approval letter G160208-S003.Letter.NEWS.APPR (002).pdf

Evaluation Form Home based tDCS in MDD_Caregiver-administrator.docx

Revised CPQ_v1.docx

Proxy and Medical care Info.792019.docx

Evaluation Form Home based tDCS in MDD_v2PMDD.docx

PhoneScreenQuestionnaire_Caregiver-administrator_clean.docx

PhoneScreenQuestionnaire_PMDD_v2_5420.docx

tDCS Eligibility Questionnaire_41220.docx

Home based tDCS MDD Training Manual v5 5120.docx

MADRS.pdf

Evaluation Form Home based tDCS in MDD_v2PMDD.docx

Caregiver-administrator tDCS Competency Checklist_1 5120