Medical University of South Carolina

Accelerated High-Dose Transcranial Direct Current Stimulation (tDCS) for Depression: An Open-Label Outpatient Pilot Study

ClinicalTrials.gov Identifier (NCT Number): NCT

SPONSOR / COLLABORATORS:

- Medical University of South Carolina (MUSC)
- City College of New York (Collaborating Investigator: Marom Bikson, PhD)

PRINCIPAL INVESTIGATOR:

Mark S. George, MD
Distinguished Professor, Psychiatry, Radiology, and Neuroscience
Medical University of South Carolina

Study Lead: Clayton Olash, MD

Psychiatry Resident

DART Fellow

PROTOCOL VERSION: Version 2.1
Date of Document: November 4, 2025

DOCUMENT TYPE: Full Study Protocol

PRINCIPAL INVESTIGATOR: Mark George, MD [1]

CO-INVESTIGATORS: Clayton Olash, MD,[1] Danyal Smani, MD,[1] Stewart Cox, MD, PhD[1], Marom Bikson, PhD[2], Kyle Donnery, PhD, Jean-Philippe Miron, MD, PhD[3], John Freedy, MD, PhD[4], Mark George, MD[1]

[1] Brain Stimulation Laboratory, Medical University of South Carolina

[2] City College of New York (CCNY) Neural Engineering Group

[3] Interventional Psychiatry Program, UC San Diego Health

[4] Medical University of South Carolina, Department of Family Medicine

1.0 Objectives / Specific Aims

Aim 1: Evaluate the Safety, Feasibility, and Tolerability of High-Dose Repeated tDCS in Adults with Major Depressive Disorder

Aim 1:

To evaluate the safety, tolerability, and feasibility of delivering high-dose transcranial direct current stimulation (tDCS) at 6 mA, administered twice daily for five consecutive days in an outpatient brain stimulation laboratory setting. Safety will be assessed by the absence of device-related serious adverse events (SAEs) (Protections (OHRP), 2010) requiring hospitalization or emergency care, and by skin assessments at each visit. Tolerability will be operationalized using the standardized tDCS Adverse Event Questionnaire (A. Brunoni et al., 2011). We hypothesize that ≥80% of participants will meet the "tolerated" classification, no device-related SAEs will occur, and the independent Safety Review Committee will not recommend stopping the study after reviewing safety/tolerability data from the first three participants in the run-in cohort.

Aim 2: Collect Preliminary Outcome Data on Depression Symptom Improvement and Mindfulness Following High-Dose Repeated tDC

This aim will explore whether high-dose, twice-daily transcranial direct current stimulation (tDCS) administered over five consecutive days leads to measurable improvements in depressive symptoms and state mindfulness. All participants (n = 20) will complete validated pre- and post-treatment clinical assessments, including the Patient Health Questionnaire-9 (PHQ-9) and the Snaith-Hamilton Pleasure Scale (SHAPS), to evaluate changes in mood and anhedonia. Additionally, participants will complete the Cognitive and Affective Mindfulness Revised (CAMS-R) before and after the intervention to assess changes in state mindfulness. Finally, we will also assess potential cognitive effects—both positive and negative—on working memory,

attention, and processing speed using the PROMIS Cognitive Function measure and the Trail Making Test. While this study is not powered to test efficacy, these exploratory data will help estimate effect sizes and inform the design of a future randomized controlled trial. We hypothesize that participants will show reductions in depressive symptoms, improvements in hedonic tone, and increases in state mindfulness following the stimulation protocol.

Aim 3: E-Field Modeling

All participants will undergo a structural MRI to enable individualized retrospective E-field modeling. This modeling will estimate intracerebral current flow and assess the relationship between predicted dose and tolerability or symptom change. E-field modeling is exploratory and will serve to inform potential future dose-response modeling and precision targeting in follow-up studies.

2.0 Background

Major Depressive Disorder (MDD) is a highly debilitating condition characterized by persistent sadness, impaired functioning, and significant morbidity, profoundly impacting individuals' quality of life and societal productivity (Stringaris, 2017). Despite advances in pharmacological and psychotherapeutic treatments, current estimates suggest that about 20-40% of patients continue to experience inadequate symptom relief (Touloumis, 2021).

Neuromodulation techniques, including transcranial direct current stimulation (tDCS), have emerged as effective alternatives or adjuncts for managing depressive symptoms. Numerous randomized controlled trials and meta-analyses have shown tDCS to be effective in alleviating acute depressive episodes, demonstrating moderate effect sizes across many studies (A. R. Brunoni et al., 2016; Couture et al., 2025; Moffa et al., 2020; Palm et al., 2016; Zheng et al., 2024). However, in spite of these findings listed above, tDCS has yet to achieve widespread clinical adoption or FDA approval, likely due to several high-profile randomized controlled trials that failed to differentiate either active treatment from sham stimulation (Blumberger et al., 2012; Loo et al., 2010, 2018) or noninferiority from the gold standard of antidepressant treatment (A. R. Brunoni et al., 2017). Contributing factors to these failed studies likely include: insufficient dose or short course length (Loo et al., 2010), treatment-resistant populations (Blumberger et al., 2012), active sham designs (Loo et al., 2018), and multisite variability with protocol heterogeneity (Loo et al., 2018). Furthermore, a review of the literature indicates that, in general, higher tDCS intensities — for example, 2 mA compared to 1 mA — are associated with greater clinical effects across a range of neuropsychiatric conditions (A. R. Brunoni et al., 2016; Evans et al., 2020; Moffa et al., 2020; Salehinejad et al., 2020; Zheng et al., 2024). In addition, recent studies employing accelerated protocols, higher cumulative total duration/dosing, and repeated daily sessions have demonstrated superior clinical outcomes (Couture et al., 2025; Moirand et al., 2022; Woodham et al., 2025), echoing innovations seen in TMS research with the high-dose SAINT protocol (Cole et al., 2022).

Nevertheless, the vast majority of clinical studies to date have limited stimulation intensity to ≤2 mA, despite substantial variability in the actual internal dose delivered to cortical tissue due to

individual differences in anatomy, scalp, and skull conductivity (Evans et al., 2020). This variability means that two individuals receiving the same applied current may experience markedly different effective brain doses, leaving the safety, tolerability, and potential efficacy of higher intensities largely untested. To address this gap, this study will look to establish the safety, tolerability, and feasibility of delivering repeated dosing at 6 mA stimulation using a modified Soterix Medical HC-1x1 tDCS system with high-capacity hydrogel electrodes in patients with MDD.

Recent dose-escalation studies in brain injury populations have confirmed safety and tolerability at 4 mA (Chhatbar et al., 2017; Nitsche & Bikson, 2017), while recent assessments tested with healthy volunteers indicate minimal discomfort and no significant skin injury even at 6 mA (Donnery et al., 2025). However, this device and dose have not been tested in a clinical or depressive patient population. Establishing feasibility and safety under these clinical conditions is critical to progressing toward a definitive efficacy randomized controlled trial (RCT) and expanding the therapeutic reach of tDCS for treating Major Depressive Disorder.

3.0 Intervention to be Studied

The intervention we are studying is called high-dose transcranial direct current stimulation (tDCS). tDCS is a non-invasive form of neuromodulation that delivers a low-intensity electrical current through electrodes placed on the scalp to modulate cortical excitability. The device used in this trial is a modified version of the Soterix Medical 1x1 tDCS system, a platform with a strong safety record and use in hundreds of clinical trials worldwide. The modified "High Capacity" (HC-1x1) version in this study will be configured to deliver up to 6 mA of current with a ramp-up period extended from 60 seconds to 120 seconds to enhance comfort. In addition, the maximum voltage will be reduced approximately fivefold to improve tolerability further.

Stimulation will be delivered using self-adhesive hydrogel electrodes manufactured in the laboratory of Dr. Marom Bikson, connected to the output of the modified 1x1 device. Electrodes will be positioned in a bifrontal montage, with the anode over the left frontal region and the cathode over the right frontal region. The device will be activated for 20 minutes per session, with twice-daily sessions separated by at least 30 minutes during the main protocol phase.

4.0 Study Endpoints

Aim 1 Primary Endpoint: *Safety, Feasibility, and Tolerability*

The proportion of participants meeting the "tolerated" classification as defined in Aim 1, based on data from the standardized tDCS Adverse Event Questionnaire and skin integrity assessments. "Tolerated" is defined as:

1. Completion of all scheduled tDCS sessions without discontinuation due to adverse events

2. No device-related serious adverse events (SAEs) requiring hospitalization or emergency care

3. No more than one transient Severe/Extreme symptom (score 4–5 on Likert scale) lasting ≤30 minutes without intervention

4. No clinically significant skin irritation, defined as skin redness ≥3 persisting >24 hours or requiring medical treatment.

Secondary Endpoints:

- Determination by the independent Safety Review Committee, after review of safety/tolerability data from the first three participants in the safety run-in cohort, to proceed with full enrollment.

- Recruitment rate from primary care referrals

- Proportion of participants completing all scheduled sessions

- Average symptom severity scores from the tDCS Adverse Event Questionnaire across all participants

Aim 2 Primary Endpoint: *Neuropsychiatric Assessments with a focus on depression, anxiety, cognitive function, and mindfulness*.A neuropsychiatric battery will be collected at baseline, immediately post-intervention (Day 5), and at four-week follow-up. This battery will include the following validated measures:

- **Patient Health Questionnaire-9 (PHQ-9)** – for self-reported depression severity.
  – to examine state mindfulness and experiential changes.

- **Cognitive and Affective Mindfulness Revised (CAMS-R)**

- **Snaith-Hamilton Pleasure Scale (SHAPS)** – to measure anhedonia
- **Trail Making Test (TMT) Parts A & B- To measure objective changes in cognitive processing, such as working memory, attention, and concentration**
- **PROMIS Cognitive Function Test 4a- to measure subjective changes in cognitive function such as memory**

Aim 3 Primary Endpoint: *MRI and Retrospective E-field Modeling*

Participants will undergo MRI scanning for retrospective electric field (E-field) modeling analyses, conducted in collaboration with Dr. Bikson's laboratory at CCNY. This secondary outcome will provide important mechanistic insight into electric field distribution and dose-response relationships relevant to clinical outcomes.

5.0 Inclusion & Exclusion Criteria / Study Population

This study seeks to recruit from a broad range of individuals to ensure generalizability, though some exclusion criteria are required to ensure participant safety. Participants will be screened. The recruited sample will be 50% female. No racial or ethnic groups will be excluded during recruitment, nor will any other individuals with diverse backgrounds. However, participants must be English-speaking, as the study consent and other assessments are presented in English. Risks of tDCS to a fetus are currently unknown. Thus, women of childbearing age will be screened for pregnancy during the screening assessment and will be provided a pregnancy test prior to stimulation to confirm they are not pregnant.

Inclusion Criteria

- Ages 18–70.
- Current MDD diagnosis (MINI v7).
- Baseline PHQ-9 > 9.
- Capacity to consent
- Fluent English.

Exclusion Criteria

- Current or past diagnosis of treatment-resistant depression, defined as failure of ≥2 adequate antidepressant trials at any point. If on an antidepressant: Must be on a stable dose for ≥4 months prior to enrollment. No medication changes (dose or agent) during the study period.
- Bipolar or psychotic disorder
- Primary anxiety disorders without concomitant major depression as defined above
- Current significant suicidal ideation or behaviors require a higher level of care.
- Diagnosis of personality disorder
- Use of neuromodulation therapies (e.g., ECT, TMS, VNS) within the past 6 months.
- History of seizures, implanted cranial/ cardiac metal, or neurosurgery.
- Frequent and or severe headache
- Must be not have any contraindication to MRI (e.g. metals, implants, etc.)
- Personal history of head trauma, concussion, or TBI
- Current alcohol or substance-use disorder (moderate-severe).
- Any non-uniformities in the skin under the electrode site, including eczema, severe rashes, hyperhidrosis, communicable skin disorders, sensitive skin (ex., eczema, severe rashes), blisters, open wounds, burns, including sunburns, cuts or irritation (e.g., due to shaving), or other skin defects or lesions, as determined by clinical personnel
- Pregnancy (urine test required for women of childbearing potential).

6.0 Number of Subjects

A total of N = 20 participants will be enrolled in a structured, two-phase study evaluating safety, tolerability, feasibility, and exploratory efficacy of a novel high-dose transcranial direct current stimulation (tDCS) protocol. We will recruit and aim to enroll 20 participants for an expected 12 total completed participants.

7.0 Setting

Study activities will occur in two primary settings: the MUSC Brain Stimulation Laboratory Space and the MRI scanner at MUSC. The stimulations will take place in the Brain Stimulation Lab (5th Floor, MUSC Institute of Psychiatry), a secure outpatient neuromodulation suite equipped with adjustable treatment chairs, video monitoring, crash cart access, and on-site clinical supervision. Participants check in through the IOP outpatient research desk and are escorted to the badge-secured lab, where licensed research staff will be present.

For participants undergoing E-field modeling, MRI scans will be performed at the MUSC Center for Biomedical Imaging (CBI) located at 30 Bee Street, 29425, and de-identified for retrospective analysis by Dr. Bikson's lab at CCNY.

8.0 Recruitment Methods

Recruitment for this study will be conducted through the Family Medicine Primary Care Clinics at MUSC, under the management of Dr. John Freedy. Primary care physicians in these clinics will identify patients with a diagnosis of depression who may be appropriate for participation. Physicians will conduct an initial screen against the study's inclusion and exclusion criteria. If a patient appears to meet preliminary eligibility requirements, and expresses interest in the study, the physician will notify the Principal Investigator and study collaborators. The research team will then follow up with the patient to confirm eligibility, provide study information, and obtain informed consent prior to enrollment.

In addition, we will also be recruiting through paper flyers and advertisements on social media such as Instagram, targeting patients in the Charleston community who may meet our inclusion and exclusion criteria. The advertisement will have information on how to reach out to a member of our team, who will then thoroughly screen them before, if applicable, consenting the participant.

9.0 Consent Process

Written informed consent will be obtained either in a private room at MUSC, or in a secure location of their choosing. For patients that are unable to arrive at the lab prior to the start of the study, electronic "eConsent" will also be available. Participants will receive a copy of the consent form, either paper or electronic. Consent covers procedures, time commitment, risks/benefits, confidentiality, voluntary participation, and right to withdraw, of which the study team will describe thoroughly

In addition, participants will be prompted to ask questions throughout the consent process to further ensure understanding. Participants will be given ample time to ask questions and consider participation. After signing the consent form, they will also be offered a hard copy.

10.0 Study Design / Methods

At the initial study visit, participants will undergo the informed consent process with a co-investigator. After providing written consent, participants will complete baseline

neuropsychological assessments, including the standardized tDCS Adverse Event Questionnaire, the PHQ-9, the SHAPS, and the CAMS-R. A pregnancy screening will also be conducted when applicable. Following these assessments, participants will be escorted to a room in the brain stimulation lab on the 5th floor to undergo their first tDCS stimulation session. Since MRI is being obtained for E-field modeling, and not pre vs post, the MRI can be scheduled at any point and does not have to be obtained before or during the study.

Day 1 (dose-escalation safety assessment cohort: first 3 patients enrolled):

- 20-minute stimulation at **2 mA** → 30-minute rest period (extendable to 60 minutes if needed)
- 20-minute stimulation at **4 mA** → 30-minute rest period (extendable to 60 minutes if needed)
- 20-minute stimulation at **6 mA**

Day 2 (skin integrity and safety check):

- Visual inspection of electrode sites for erythema, burns, or other skin reactions, and completion of the tDCS Adverse Event Questionnaire
- If no **serious adverse event (SAE)** requiring emergency department evaluation or hospitalization is observed, and skin integrity is deemed acceptable by clinical evaluation by on-site MD, participants will proceed to:
    - Two 20-minute stimulation sessions at **6 mA**, separated by a 30-minute-60 to 60-minute rest period for the remaining 4 days.
    - **Main Protocol (remaining 9 participants)**: Progression beyond the initial safety run-in cohort will occur only after the Safety Review Committee has reviewed the adverse event data, skin integrity assessments, and tolerability questionnaire responses from the first three participants and determined that continuation at 6 mA is acceptable.
        - Same procedure as above, including consent, neuropsychological testing, pregnancy testing (if applicable), and MRI
        - Instead of starting at 2 mA, participants will start at 2 sessions/day at 6 mA (20 min each, 30-minute interval),
        - Conducted in-lab over 5 consecutive weekdays. After each session, skin and safety checks will be completed by study staff or trained personnel.
- **Post-Treatment Assessment**:

- Conducted in-person after the last stimulation session
- Virtual follow-up at 4 weeks to assess durability. Pt's will answer the same neuropsychological questions as above.

12.0 Data Management

All data will be stored in the REDCap database. Information about the participant (including their identifiable private information) may have all their identifiers removed and used for future research studies or distributed to other researchers for future research without additional informed consent. After participation, REDCap data will be downloaded in Excel format to the secure MUSC server. In terms of publication, data will be published in aggregate form, so individual participants will not be identifiable in the final manuscript. No identifying information will be published.

Confidentiality and Quality Control: All study personnel will complete Social-Behavioral-Educational research CITI training, and also complete in-lab training regarding data security practices. Study personnel will be trained in the IRB protocol. The investigator and co-investigators will be available to monitor data collection to ensure quality, confidentiality, and adherence to the IRB protocol.

13.0 Provisions to Monitor Data & Ensure Safety

The Principal Investigator (PI), or a designated Co-Investigator (Co-I) if the PI is unavailable, will be responsible for reporting all unanticipated problems or adverse events (AEs) promptly to the Institutional Review Board (IRB). The PI or designated study team member will be present during each stimulation session to document any AEs in real-time. Screening data collected from participants will be securely stored in REDCap. Data from participants who do not qualify for the study will be securely destroyed.

The PI or Co-I will oversee device testing and the technical use of the High-Capacity tDCS (HC-tDCS) device. Participants will remain in the lab throughout the stimulation protocol, monitored continuously by study personnel and research staff. Co-Investigators will be present for all administration sessions, and participants will be closely monitored around the clock for any adverse events and tolerability concerns.

Informed consent will be obtained by the PI or Co-I, ensuring participants are fully informed about the research procedures, time requirements, potential risks and benefits, their rights to refuse or withdraw from participation at any time without prejudice, and providing contact details for the principal investigator.

Participant confidentiality will be rigorously maintained, with access to collected data strictly limited to authorized research staff. Participants' identities in databases will be protected using

alphanumeric codes, and all data will be securely stored in locked file cabinets or on secure servers accessible only by designated members of the study team.

14.0 Withdrawal of Subjects

Subjects may withdraw at any time without penalty. Reasons and partial data will be documented. Participants who withdraw due to AEs will receive appropriate medical evaluation.

15.0 Risks to Subjects

Transcranial direct current stimulation (tDCS) has been shown to safe when used within standard parameters (up to 4 mA, sessions under 40–60 minutes), with no evidence of serious or irreversible adverse effects reported across tens of thousands of sessions, including in vulnerable populations such as children, the elderly, and patients with neurological conditions (Bikson et al., 2016; Grossman et al., 2019; Ko, 2021). Furthermore, this newly invented High-Capacity tDCS device was recently studied in healthy volunteers and found to be tolerated and safe up to 6 mA for 30 minutes, with minimal discomfort and no skin injury (Donnery et al., 2025). The most commonly reported side effects in tCDS research are mild and transient, including itching, tingling, headache, burning sensations, and discomfort at the site of electrode placement, with these effects occurring at similar rates in both active and sham (placebo) groups (Aparicio et al., 2016; A. Brunoni et al., 2011; Nikolin et al., 2017). There is no evidence that repeated sessions increase the risk of adverse events, nor that any specific patient group is at higher risk under standard protocols (Chhatbar et al., 2017; Russo et al., 2017). Animal studies suggest that the electrical doses used in tDCS are far below levels that could cause brain tissue damage (Bikson et al., 2016; Ko, 2021).

1. **Transient Skin Erythema / Redness**
   Local redness or mild warmth is common beneath the stimulation pads. This reaction is expected to resolve within 30–60 minutes. Participants will be advised to apply vitamin E or an aloe-based cream if erythema persists longer than 2 hours. Any Grade ≥ 2 skin event will be documented and reviewed prior to the next stimulation day.
2. **Skin Irritation, Dermatitis, or Superficial Burns**
   Prolonged or repeated sessions at higher current density may produce focal irritation, itching, or—rarely—superficial burn/necrosis. All electrode sites will be inspected before and after each session.
3. **Tingling, Itching, or Pressure Sensation**
   Mild paresthesia under the pads (described as tingling, itching, or pressure) is typical and generally subsides shortly after the current is offset.
4. **Headache, Dizziness, or Facial Pain**
   Low-intensity electrical stimulation of the scalp can occasionally provoke a headache or transient dizziness. These symptoms usually resolve within minutes. Participants will be seated during stimulation to minimize fall risk; fluids and rest will be offered if symptoms persist.
5. **Mood Destabilization or Induction of Mania**
   Although rare, neuromodulation studies in depression have reported emergent hypomanic or manic symptoms. Systematic reviews and meta-analyses have documented a small

number of cases—six instances of affective switching (from depression to mania or hypomania) were observed in studies of tDCS for bipolar depression, and a total of 11 cases have been reported in patients with depression across the literature, though the overall incidence is very low and a direct causal relationship is difficult to establish due to the limited number of subjects and events (Antal et al., 2017; A. R. Brunoni et al., 2017; Dondé et al., 2017; Matsumoto & Ugawa, 2016). Participants will complete brief mood screens daily; any sign of treatment-emergent mania will prompt psychiatric evaluation and possible withdrawal from the study.

6. **Seizure**
   The delivered current (≤ 6 mA) and charge density are well below established seizure thresholds; nonetheless, a new-onset seizure is considered a Serious Adverse Event (SAE). In our review of the literature, there is only one case report of a tCDS being associated with seizure, and this was in a child with epilepsy (Ekici, 2015). Emergency response equipment and ACLS-trained personnel will be immediately available; the IRB will be notified within 24 hours of any seizure.
7. **Cardiovascular Changes**
   Transcranial direct current stimulation is not typically associated with heart-rate variability, but autonomic shifts cannot be ruled out. Vital signs will be obtained pre-session and once hourly during Days 1–7. Clinically significant hypotension/bradycardia (≥ 20 % decline from baseline) will lead to dose reduction or discontinuation.
8. **Device Malfunction**
   Unintended rapid discharge or incomplete current delivery could result from device failure. Any malfunctioning of the device will be uploaded to RedCaps. Malfunctioning devices will be removed and quarantined for engineering review.
9. **Unknown Risks**
   HC-tDCS is a novel, higher-dose form factor; unanticipated AEs are possible. New information that could alter the risk–benefit profile will be promptly communicated to participants and the IRB.
10. **Loss of Confidentiality**
    As with any study collecting personal data, there is a small risk of a privacy breach. Data protections (encrypted REDCap, coded identifiers, limited-access servers) are in place, and any breach would be reported per MUSC policy.
11. **Questionnaire-Related Distress**
    Some survey items address depressive symptoms and suicidal ideation. Participants may skip any item or discontinue assessments; immediate clinical support from study psychiatrists is available.

16.0 Potential Benefits

To the Participant: Participants may experience improvement in depressive symptoms as a result of receiving high-dose transcranial direct current stimulation (tDCS). While the primary purpose of this study is to evaluate safety, tolerability, and feasibility, tDCS has been shown in prior research to produce clinically meaningful reductions in depressive symptoms, particularly in non-treatment-resistant populations. Participants will receive repeated, structured stimulation sessions under close clinical supervision, and their mood, anxiety, and related symptoms will be regularly monitored. This may allow for earlier identification of symptom changes and facilitate appropriate clinical follow-up if needed. Although symptom improvement cannot be guaranteed,

participants may benefit from access to a novel, non-pharmacologic intervention that is not yet widely available in clinical settings.

To Society: If shown to be safe, tolerable, and feasible, this study could lay the groundwork for a scalable, accessible brain stimulation intervention for Major Depressive Disorder. Current neuromodulation treatments are generally limited to treatment-resistant populations and require in-clinic administration, restricting their accessibility. The findings from this study could inform larger efficacy trials and ultimately contribute to the development of a first-line, non-pharmacologic treatment option that could be deployed in primary care and outpatient psychiatry settings. Such a treatment could expand the therapeutic toolkit for depression, reduce reliance on medications with systemic side effects, and improve the quality of life for a broad range of patients.

17.0 Sharing of Results with Subjects

Aggregate results will be posted on ClinicalTrials.gov and shared upon request. Clinically actionable incidental findings will be communicated individually.

18.0 Drugs or Devices

The device used in this trial is a modified version of the Soterix Medical 1x1 tDCS system, a platform with a strong safety record and use in hundreds of clinical trials worldwide. The modified "High Capacity" (HC-1x1) version in this study will be configured to deliver up to 6 mA of current with a ramp-up period extended from 60 seconds to 120 seconds to enhance comfort. In addition, the maximum voltage will be reduced approximately fivefold to further improve tolerability.

Stimulation will be delivered using self-adhesive hydrogel electrodes manufactured in the laboratory of Dr. Marom Bikson, connected to the output of the modified 1x1 device. Electrodes will be positioned in a bifrontal montage, with the anode over the left frontal region and the cathode over the right frontal region. The device will be activated for 20 minutes per session, with twice-daily sessions separated by at least 30 minutes during the main protocol phase.

tDCS is a non-significant risk method that has been approved in many studies by the MUSC IRB, of which Dr. Mark George has been a co-author (Borckardt et al., 2012; George & Aston-Jones, 2010; Glaser et al., 2016). The intervention under investigation involves the use of a tDCS hydrogel electrode (High Capacity, HC). Compared to the typical sponge electrodes, HC electrodes are designed for superior delivery of current across the skin, which in turn reduces the sensations felt at the skin, allowing the use of higher current, for example, 6 mA. Based on tDCS safety studies and standards, while most trials use 2 mA, this is not a safety limit but rather related to skin sensations. 6 mA remains well below safety limits reported (~50 mA) (Bikson et al., 2016). In regard to electrode current density and charge density, HC-tDCS with 6 mA is less than "High Definition tDCS," which is also well established to be safe, including trials at MUSC

(Borckardt et al., 2012). Based on the prior work in healthy subjects, we expect 6 mA HD-tDCS to be well tolerated in a clinical population of MDD.

The device used for this study is the Soterix Medical 1x1 HC-tDCS device, which is a medical-grade investigational device (ie, not approved by the FDA for treatment of any disease). The 1x1 HC-tDCS device is based on the Soterix Medical 1x1 tDCS platform, which has been used in hundreds of clinical trials under NSR, is CE marked, and broadly considered a quality standard in tES. The standard models have been modified to allow the higher current needed in the trial, along with a slower ramp and reduced voltage compliance to further enhance tolerability.

19.0 References

Antal, A., Alekseichuk, I., Bikson, M., Brockmöller, J., Brunoni, A., Chen, R., Cohen, L., Dowthwaite, G., Ellrich, J., Flöel, A., Fregni, F., George, M., Hamilton, R., Haueisen, J., Herrmann, C., Hummel, F., Lefaucheur, J., Liebetanz, D., Loo, C., … Paulus, W. (2017). Low intensity transcranial electric stimulation: Safety, ethical, legal regulatory and application guidelines. *Clinical Neurophysiology*, *128*, 1774–1809. https://doi.org/10.1016/j.clinph.2017.06.001

Aparicio, L., Guarienti, F., Razza, L., Carvalho, A., Fregni, F., & Brunoni, A. (2016). A Systematic Review on the Acceptability and Tolerability of Transcranial Direct Current Stimulation Treatment in Neuropsychiatry Trials. *Brain Stimulation*, *9*, 671–681. https://doi.org/10.1016/j.brs.2016.05.004

Bikson, M., Grossman, P., Thomas, C., Zannou, A., Jiang, J., Adnan, T., Mourdoukoutas, A., Kronberg, G., Truong, D., Boggio, P., Brunoni, A., Charvet, L., Fregni, F., Fritsch, B., Gillick, B., Hamilton, R., Hampstead, B., Jankord, R., Kirton, A., … Woods, A. (2016). Safety of Transcranial Direct Current Stimulation: Evidence Based Update 2016. *Brain Stimulation*, *9*, 641–661. https://doi.org/10.1016/j.brs.2016.06.004

Blumberger, D. M., Tran, L. C., Fitzgerald, P. B., Hoy, K. E., & Daskalakis, Z. J. (2012). A Randomized Double-Blind Sham-Controlled Study of Transcranial Direct Current

Stimulation for Treatment-Resistant Major Depression. *Frontiers in Psychiatry*, *3*, 74. https://doi.org/10.3389/fpsyt.2012.00074

Borckardt, J. J., Bikson, M., Frohman, H., Reeves, S. T., Datta, A., Bansal, V., Madan, A., Barth, K., & George, M. S. (2012a). A pilot study of the tolerability and effects of high-definition transcranial direct current stimulation (HD-tDCS) on pain perception. *The Journal of Pain*, *13*(2), 112–120.

Borckardt, J. J., Bikson, M., Frohman, H., Reeves, S. T., Datta, A., Bansal, V., Madan, A., Barth, K., & George, M. S. (2012b). A pilot study of the tolerability and effects of high-definition transcranial direct current stimulation (HD-tDCS) on pain perception. *The Journal of Pain*, *13*(2), 112–120. https://doi.org/10.1016/j.jpain.2011.07.001

Brunoni, A., Amadera, J., Berbel, B., Volz, M., Rizzerio, B. G., & Fregni, F. (2011). A systematic review on reporting and assessment of adverse effects associated with transcranial direct current stimulation. *The International Journal of Neuropsychopharmacology*, *14 8*, 1133–1145. https://doi.org/10.1017/S1461145710001690

Brunoni, A. R., Moffa, A. H., Fregni, F., Palm, U., Padberg, F., Blumberger, D. M., Daskalakis, Z. J., Bennabi, D., Haffen, E., Alonzo, A., & Loo, C. K. (2016). Transcranial direct current stimulation for acute major depressive episodes: Meta-analysis of individual patient data. *The British Journal of Psychiatry*, *208*(6), 522–531. https://doi.org/10.1192/bjp.bp.115.164715

Brunoni, A. R., Moffa, A. H., Sampaio-Junior, B., Borrione, L., Moreno, M. L., Fernandes, R. A., Veronezi, B. P., Nogueira, B. S., Aparicio, L. V. M., Razza, L. B., Chamorro, R., Tort, L. C., Fraguas, R., Lotufo, P. A., Gattaz, W. F., Fregni, F., & Benseñor, I. M. (2017). Trial of Electrical Direct-Current Therapy versus Escitalopram for Depression. *New England Journal of Medicine*, *376*(26), 2523–2533. https://doi.org/10.1056/NEJMoa1612999

Chhatbar, P. Y., Chen, R., Deardorff, R., Dellenbach, B., Kautz, S. A., George, M. S., & Feng,

W. (2017). Safety and tolerability of transcranial direct current stimulation to stroke patients—A phase I current escalation study. *Brain Stimulation*, *10*(3), 553–559. https://doi.org/10.1016/j.brs.2017.02.007

Cole, E. J., Phillips, A. L., Bentzley, B. S., Stimpson, K. H., Nejad, R., Barmak, F., Veerapal, C., Khan, N., Cherian, K., Felber, E., Brown, R., Choi, E., King, S., Pankow, H., Bishop, J. H., Azeez, A., Coetzee, J., Rapier, R., Odenwald, N., … Williams, N. R. (2022). Stanford Neuromodulation Therapy (SNT): A Double-Blind Randomized Controlled Trial. *The American Journal of Psychiatry*, *179*(2), 132–141. https://doi.org/10.1176/appi.ajp.2021.20101429

Couture, M., Desbeaumes Jodoin, V., Bousseau, E., Sarshoghi, A., Nitsche, M. A., Blumberger, D. M., Bolduc, C., Weissman, C. R., Appelbaum, L. G., Daskalakis, Z. J., Poorganji, M., Lespérance, P., & Miron, J.-P. (2025). Spaced Transcranial Direct Current Stimulation for Major Depression. *The American Journal of Psychiatry*, *182*(3), 276–284. https://doi.org/10.1176/appi.ajp.20240083

Dondé, C., Amad, A., Nieto, I., Brunoni, A., Neufeld, N., Bellivier, F., Poulet, E., & Geoffroy, P. (2017). Transcranial direct-current stimulation (tDCS) for bipolar depression: A systematic review and meta-analysis. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *78*, 123–131. https://doi.org/10.1016/j.pnpbp.2017.05.021

Donnery, K., FallahRad, M., Khadka, N., Saw, M., Babaev, B., Osorio, S., Koochesfahani, M. B., Bhuiyan, R., Elwassif, J. M., & Bikson, M. (2025). *High-Capacity transcranial Direct Current Stimulation (HC-tDCS)* (p. 2025.06.11.659142). bioRxiv. https://doi.org/10.1101/2025.06.11.659142

Ekici, B. (2015). Transcranial Direct Current Stimulation–Induced Seizure. *Clinical EEG and Neuroscience*, *46*, 169–169. https://doi.org/10.1177/1550059414540647

Evans, C., Bachmann, C., Lee, J. S. A., Gregoriou, E., Ward, N., & Bestmann, S. (2020). Dose-controlled tDCS reduces electric field intensity variability at a cortical target site. *Brain*

Stimulation: Basic, Translational, and Clinical Research in Neuromodulation, *13*(1), 125–136. https://doi.org/10.1016/j.brs.2019.10.004

George, M. S., & Aston-Jones, G. (2010). Noninvasive techniques for probing neurocircuitry and treating illness: Vagus nerve stimulation (VNS), transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS). *Neuropsychopharmacology*, *35*(1), 301–316. https://doi.org/10.1038/npp.2009.87

Glaser, J., Reeves, S. T., Stoll, W. D., Epperson, T. I., Hilbert, M., Madan, A., George, M. S., & Borckardt, J. J. (2016). Motor/Prefrontal Transcranial Direct Current Stimulation (tDCS) Following Lumbar Surgery Reduces Postoperative Analgesia Use. *Spine*, *41*(10), 835. https://doi.org/10.1097/BRS.0000000000001525

Grossman, P., Woods, A., Knotkova, H., & Bikson, M. (2019). Safety of Transcranial Direct Current Stimulation. *Practical Guide to Transcranial Direct Current Stimulation*. https://doi.org/10.1007/978-3-319-95948-1_6

Ko, M. (2021). Safety of Transcranial Direct Current Stimulation in Neurorehabilitation. *Brain & NeuroRehabilitation*, *14*. https://doi.org/10.12786/bn.2021.14.e9

Loo, C. K., Husain, M. M., McDonald, W. M., Aaronson, S., O'Reardon, J. P., Alonzo, A., Weickert, C. S., Martin, D. M., McClintock, S. M., Mohan, A., & Lisanby, S. H. (2018). International randomized-controlled trial of transcranial Direct Current Stimulation in depression. *Brain Stimulation*, *11*(1), 125–133. https://doi.org/10.1016/j.brs.2017.10.011

Loo, C. K., Sachdev, P., Martin, D., Pigot, M., Alonzo, A., Malhi, G. S., Lagopoulos, J., & Mitchell, P. (2010). A double-blind, sham-controlled trial of transcranial direct current stimulation for the treatment of depression. *The International Journal of Neuropsychopharmacology*, *13*(1), 61–69. https://doi.org/10.1017/S1461145709990411

Matsumoto, H., & Ugawa, Y. (2016). Adverse events of tDCS and tACS: A review. *Clinical Neurophysiology Practice*, *2*, 19–25. https://doi.org/10.1016/j.cnp.2016.12.003

Moffa, A. H., Martin, D., Alonzo, A., Bennabi, D., Blumberger, D. M., Benseñor, I. M.,

Daskalakis, Z., Fregni, F., Haffen, E., Lisanby, S. H., Padberg, F., Palm, U., Razza, L. B., Sampaio-Jr, B., Loo, C., & Brunoni, A. R. (2020). Efficacy and acceptability of transcranial direct current stimulation (tDCS) for major depressive disorder: An individual patient data meta-analysis. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *99*, 109836. https://doi.org/10.1016/j.pnpbp.2019.109836

Moirand, R., Imbert, L., Haesebaert, F., Chesnoy, G., Bediou, B., Poulet, E., & Brunelin, J. (2022). Ten Sessions of 30 Min tDCS over 5 Days to Achieve Remission in Depression: A Randomized Pilot Study. *Journal of Clinical Medicine*, *11*(3), 782. https://doi.org/10.3390/jcm11030782

Nikolin, S., Huggins, C., Martin, D., Alonzo, A., & Loo, C. (2017). Safety of repeated sessions of transcranial direct current stimulation: A systematic review. *Brain Stimulation*, *11*, 278–288. https://doi.org/10.1016/j.brs.2017.10.020

Nitsche, M. A., & Bikson, M. (2017). Extending the parameter range for tDCS: Safety and tolerability of 4 mA stimulation. *Brain Stimulation*, *10*(3), 541–542. https://doi.org/10.1016/j.brs.2017.03.002

Palm, U., Hasan, A., Strube, W., & Padberg, F. (2016). tDCS for the treatment of depression: A comprehensive review. *European Archives of Psychiatry and Clinical Neuroscience*, *266*(8), 681–694. https://doi.org/10.1007/s00406-016-0674-9

Protections (OHRP), O. for H. R. (2010, November 24). *Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events: OHRP Guidance (2007)* [Policy]. https://www.hhs.gov/ohrp/regulations-and-policy/guidance/reviewing-unanticipated-problems/index.html

Russo, C., Carneiro, M. S., Bolognini, N., & Fregni, F. (2017). Safety Review of Transcranial Direct Current Stimulation in Stroke. *Neuromodulation: Technology at the Neural Interface*, *20*. https://doi.org/10.1111/ner.12574

Salehinejad, M., Nejati, V., Mosayebi-Samani, M., Mohammadi, A., Wischnewski, M., Kuo, M.,

Avenanti, A., Vicario, C., & Nitsche, M. (2020). Transcranial Direct Current Stimulation in ADHD: A Systematic Review of Efficacy, Safety, and Protocol-induced Electrical Field Modeling Results. *Neuroscience Bulletin*, 1–22. https://doi.org/10.1007/s12264-020-00501-x

Stringaris, A. (2017). Editorial: What Is Depression? *Journal of Child Psychology and Psychiatry*, *58*(12), 1287–1289. https://doi.org/10.1111/jcpp.12844

Touloumis, C. (2021). The burden and the challenge of treatment-resistant depression. *Psychiatrike = Psychiatriki*, *32*(Supplement I), 11–14. https://doi.org/10.22365/jpsych.2021.046

Woodham, R. D., Selvaraj, S., Lajmi, N., Hobday, H., Sheehan, G., Ghazi-Noori, A.-R., Lagerberg, P. J., Rizvi, M., Kwon, S. S., Orhii, P., Maislin, D., Hernandez, L., Machado-Vieira, R., Soares, J. C., Young, A. H., & Fu, C. H. Y. (2025). Home-based transcranial direct current stimulation treatment for major depressive disorder: A fully remote phase 2 randomized sham-controlled trial. *Nature Medicine*, *31*(1), 87–95. https://doi.org/10.1038/s41591-024-03305-y

Zheng, E. Z., Wong, N. M. L., Yang, A. S. Y., & Lee, T. M. C. (2024). Evaluating the effects of tDCS on depressive and anxiety symptoms from a transdiagnostic perspective: A systematic review and meta-analysis of randomized controlled trials. *Translational Psychiatry*, *14*(1), 1–15. https://doi.org/10.1038/s41398-024-03003-w