CLINICAL TRIAL PROTOCOL

TITLE: Feasibility Study on the Use of an Intensive Transcranial Direct Current Stimulation Protocol for Major Depression

CHUM project number: 2021-9546

PRINCIPAL INVESTIGATOR:

Jean-Philippe Miron, MD, PhD(c), FRCPC
Unité de Neuromodulation Psychiatrique (UNP)
Département de psychiatrie, CHUM
Email : jean-philippe.miron.med@ssss.gouv.qc.ca

CO-INVESTIGATOR:

Paul Lespérance, MD, MSc, FRCPC
Unité de Neuromodulation Psychiatrique (UNP)
Département de psychiatrie, CHUM
Email : paul.lesperance.med@ssss.gouv.qc.ca

Chantal Bolduc, MD, FRCPC
Département de dermatologie, CHUM
Email : chantal.bolduc.med@ssss.gouv.qc.ca

COLLABORATORS:

Daniel Blumberger, MD, MSc, FRCPC
Centre for Addiction and Mental Health (CAMH), Toronto
Email: daniel.blumberger@camh.ca

Prof. Michael Nitsche, MD
IfADo Leibniz Research Centre for Working Environment and Human Factors at TU Dortmund, Allemagne
Email: nitsche@ifado.de

1.0 BACKGROUND AND RATIONALE

Major depressive disorder (MDD) is estimated to currently affect over 280 million individuals around the globe and is now ranked as the leading cause of disability worldwide (1). First-line treatments include pharmaco- and psychotherapy [2]. Even though these approaches are effective, a significant proportion of patients are left symptomatic and functionally impaired. Indeed, results from the Sequenced Treatment Alternatives to Relieve Depression Study have shown that after two (2) failed medication trials, remission rates with subsequent trials drop to 10-15% (2). Additionally, up to 50% of patients experience a chronic or recurrent course, and 30 to 40% develop treatment-resistant depression (TRD), having failed to respond to conventional treatments (3). TRD affects about 2% of the population and represents about 30 to 50% of the total treatment cost for MDD (4). Although antidepressants are convenient and simple to administer, discontinuation rates approach 50% after 3 months of use, due to concerns over side effects as much as non-response (5). Finally, intensive psychotherapy programs still achieve only 20-25% remission rates in TRD (6). Novel therapeutic approaches are therefore needed.

Non-invasive brain stimulation (NIBS) techniques, such as transcranial direct current stimulation (tDCS), have been gaining ground in the treatment of various psychiatric disorders. These non-pharmacological approaches possess an advantageous safety and tolerability profile over medication (16). Specific brain regions can be targeted using NIBS approaches, allowing modulation of the underlying dysfunctional brain networks common to various psychiatric conditions.

tDCS is an easy-to-use NIBS technique with a well-established safety and tolerability profile (7)(8) and has been the subject of multiple studies in MDD, with mixed findings (9)(10)(11). It involves the use of small electrodes directly applied to the scalp to stimulate superficial cortical areas (12). tDCS has a well-established safety and tolerability profile and has the advantage to be low-cost, easy-to-use, and portable, with even the potential to do treatments at home (9)(13). So far, some evidence supports the use of tDCS for MDD, with two large randomized controlled trials (RCTs) having been carried out by the same group, with mixed results (14) (15). For example, the landmark tDCS trial by Brunoni et al. (14) (the largest to date) compared the use of tDCS to the antidepressant escitalopram for 10 weeks in a non-inferiority trial (N = 245). Even though participants received escitalopram daily for 10 weeks (70 times overall), only 22 sessions of tDCS were offered during this period. This was in part because tDCS was administered in-clinic during those 10 weeks; the number of sessions therefore had to be limited to maximize attendance and reduce attrition.

This problem could be solved by intensive treatment. Indeed, a recent study by Michael Nitsche's group demonstrated that the effect of tDCS could be potentiated if two sessions were administered with a short break in-between, compared to a single session (16). In this study, cortical excitability induced by tDCS lasted only a few minutes when one single session was administered, while becoming prolonged up to more than 24 hours by the administration of two 20 min sessions spaced by 20 min intervals. Our group has also piloted two intensive studies using a similar type of NIBS called transcranial magnetic stimulation (TMS), where we delivered 6 (17) and 8 (18) daily sessions of TMS over a 5-day period. Treatments were safe and well-tolerated, with minimal side effects and dropout rates. Preliminary data also suggested increased clinical effects with more daily sessions. So far, this intensive approach has never been applied to tDCS. This could be due to potential concerns over adverse events (**AE**s) with such an intensive protocol, although the literature is limited on this issue. A recent review of the literature on the

therapeutic use of tDCS in humans reported no serious AEs over more than 33,200 sessions in N = 1,000 participants who received repeated sessions (≤ 40 min per session, ≤ 4 milliamps) [8]. The most reported AE is a light rash under the stimulation electrode. Rare cases of mild and temporary skin lesions have also been reported [12]-[19]; however, this was not associated with any complication [20]. In addition, a recent case study where 10 tDCS sessions were administered over 2 days reported only a mild erythema which resolved quickly after the end of stimulation [21]. Electrodes improperly soaked in saline can cause skin irritation, but this can be minimized using pre-packaged pre-soaked electrodes with an optimal amount of saline solution. Intensive tDCS protocols could be applied on a large scale given the low-cost, ease-of-use and portability of these devices.

2.0 STUDY OBJECTIVES

Primary objective: To assess the safety, tolerability, and feasibility of an intensive tDCS protocol for MDD. We hypothesize that our intensive tDCS protocol will be safe, well-tolerated and feasible.

Secondary objective: To gather preliminary data on the clinical effects of the protocol.

3.0 STUDY DESIGN

This will be a prospective, open-label, single-arm feasibility study carried over an 24-month period starting in 2022.

3.1 Study population

Participants will be recruited through referrals to our treatment clinic. We will recruit 30 outpatients 18 to 65 years of age with a diagnosis of unipolar MDD according to Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) criteria and confirmed by psychiatrists by means of the Mini-International Neuropsychiatric Interview (MINI) with a score of at least 17 on the 17-item Hamilton Depression Rating Scale (HRSD-17) as well as a low risk of suicide (Blumberger et al. 2018). Participants will be required to have had no increase or initiation of any psychotropic medication in the 4 weeks prior to screening and have normal blood work (thyroid, complete blood count, electrolytes) in the past 6 months. Exclusion criteria will be bipolar disorder, substance use disorder within the last 3 months, dementia, personality disorder, brain injury, pregnancy, specific contraindications to tDCS (e.g., intracranial implants) or previous tDCS treatment. Antidepressant use will be permitted, but anticonvulsant medication or benzodiazepine use of more than 2 mg lorazepam equivalent will not be allowed.

3.2 Intervention

Treatments will take place over 10 days (Monday to Friday). Participants will receive 5 tDCS sessions each day, for a total of 50 sessions. Each tDCS session will last 20 min at a 2 milliamps intensity and will be spaced by 20 min intervals (3h treatment block). tDCS sessions will be administered through 1x1 tES mini-CT devices (Soterix, New York, USA) already acquired by the clinic (**Fig. 1**). These devices have been used in several large MDD trials and are Health Canada approved. They are equipped with a "SNAPstrap" fixing system to reliably position the two (2) electrodes (anode and cathode). The electrodes will be placed on the scalp according to the EEG 10-20 system, with the anode in F3 and the cathode in F4. Treatment will be administered by trained research personnel and single-use “SNAPpads” pre-saturated electrodes

will be provided to participants for each treatment. These electrodes contain just the right amount of saline solution to minimize any cutaneous side-effects.

3.3 Outcomes

Participants will be initially assessed at baseline one week before treatment, on every treatment day, at the end of the last treatment day, and one and four weeks following treatment. The complete schedule is presented in **Fig. 2-3**.

Primary objective: participants will be systematically assessed every day of treatment and at follow-ups for potential AEs, and all AEs will be reported. At each treatment sessions, a safety check (i.e., visual skin examination) will be performed before and after each tDCS session, and pain levels will be assessed using a Verbal Rating Scale (VRS) of 0 to 10 (10 being the maximally tolerable amount of pain) (**Fig. 4**). Cognitive safety will also be assessed pre- and post-treatment using various tests, such as the Rey Auditory Verbal Learning Test, Rey-Osterrieth Complex Figure, Trail Making Test Parts A & B and verbal fluency test (Fig. 3). Completion and retention rates as well as the number of treatment sessions completed will be assessed. The following data will also be collected: number of potential participants referred to the study, number of patients screened, number of potential participants considered eligible, number of participants recruited, number of participants who initiated the intervention, number of treatment sessions completed, dropout rates and number of participants who completed treatment and assessments. Information on attendance in the intervention will also be measured. Regarding the secondary objective, depressive symptoms changes will be assessed through the HRSD-17, Montgomery-Asberg Depression Rating Scale (MADRS), Patient Health Questionnaire-9 (PHQ-9) and General Anxiety Disorder-7 (GAD-7) (Fig. 3). We will also use the 6-item HRSD (Fig. 3) before every treatment day and at the end of the last day, which is a highly sensitive depression scale that can be administered daily during treatment (22).

3.4 Sample size justification

No single guideline exists for pilot studies sample size calculations, with recommendations varying from 12 participants per group (23), 30 participants per group (24), 10 to 40 participants per group (25)(26) or at least 9% of the main trial's sample size (27). Using the non-central t-distribution approach devised by Julious and Owen (28)(29) and a conservative effect size of 0.5 (30), the required sample size would be of 24 participants. To account for potential dropouts, we choose a sample size of 30 participants.

3.5 Statistical analysis

Inferential statistics will be performed on baseline characteristics utilizing independent samples t-tests (two-tailed) for continuous variables and Chi-square tests for categorical variables and to summarise rates of consent, study retention, as well as data quality (completion of outcome measures and missing data). Treatment safety will be assessed by a line listing, frequency tabulations and 95% confidence intervals. We will also perform repeated measures analyses of variance (ANOVA) on mood scales score at different timepoints to assess the effect of the treatment through time. Planned repeated contrasts will be used to make comparisons between the different evaluation times. To evaluate cognitive safety of the treatment in patients, we will use the reliable change index methodology to differentiate the possible effect of the treatment on cognitive functions and outcome results due to practice effects.

3.6 Safety and adverse events

Hundreds of thousands of people have received tDCS over the last 25 years. Data available shows that tDCS is a very safe treatment with little or no side effects ((7), (8)). A recent review of the literature on the therapeutic use of tDCS in humans reported no serious AE over more than 33,200 sessions in N = 1,000 participants who received repeated sessions (≤ 40 min per session, ≤ 4 milliamps) (8). The most common of the reported side effects is ~~simply~~ a mild and temporary skin lesion under the electrode. A systematic review of 209 tDCS studies reported as side effects: itching (active treatment vs. placebo: 39.3% vs. 32.9%), tingling (22.2% vs. 18.3%), headache (14.8% vs. 16.2%), burning sensation (8.7% vs. 10.0%) and discomfort (10.4% vs. 13.4%) (31). Rare cases of mild and temporary skin lesions have also been reported (19), (12); however, the literature is reassuring to this effect (20). **In addition, a recent case study where 10 tDCS sessions were administered over 2 days reported only a mild erythema which resolved quickly after the end of stimulation (21). Rare cases of skin burn under the electrodes have been reported. These cases were usually associated** with incorrect application of the electrode or evaporation of the contact medium. Most burns were superficial and healed without scarring. As previously stated, the use of single-use "SNAPpads" pre-saturated electrodes and application by trained personnel greatly minimizes the risk of skin reaction. Across the literature, only 11 cases of manic or hypomanic switches have been reported in bipolar patients, and it is not clear that these were actually related to tDCS. tDCS has never been shown to cause cerebral edema or changes in the blood-brain barrier. tDCS causes negligible temperature changes in the skin, making thermal damage to the brain very unlikely. Electrodes improperly soaked in saline can cause skin irritation, but this can be minimized by the use of bagged electrodes pre-soaked with the optimum amount of solution such as we will use in this study. In addition, reliable data from patients who received 100 to 1000 sessions of tDCS indicate no adverse effects due to cumulative exposure. Finally, no seizures were reported in association with the use of tDCS.

Considering that very little data is available regarding intensive tDCS treatments, participants will be monitored by a dermatologist. An initial consultation will take place before the start of the treatment (Visite 2) and patients will be reassessed at the end of treatment session (visite 13). During the treatment week, high-resolution photographs of the skin will be taken daily before and after treatments and shared with the dermatologist, who will assess the treatment sites for skin lesions using a a global rating scale (0:absent to 3: severe). The dermatologist will advise the treatment team to continue or to stop treatment.

Common side effects are expected and will be recorded separately from AEs. Participants will be asked to defer any medication changes for 4 weeks before and during the course of treatment to avoid confounding effects. All AEs reported during the study will be recorded in patients' research file and include the following information: description and nature of event, onset time and date, duration, intensity, seriousness, relationship to treatment, action taken and evolution. In case of a serious adverse event, the aforementioned information will be collected in detail and will be reported to the CHUM IRB. Any AEs deemed to be related to the study by the Primary Investigator (PI), or that result in a participant's withdrawal from the study, will be followed until its resolution or until the patient is considered stable. The decision as to whether or not an AE is sufficiently severe to warrant the termination of patient treatment will be left to the clinical judgment of the (PI). A participant may also voluntarily withdraw from treatment due to what he/she perceives as an intolerable AE. If either of these occurs, the participant will be required to undergo an end-of-study assessment and will be offered appropriate care under medical supervision until the condition becomes stable.

Procedures have been developed for researchers-developers and research staff involved in managing adverse incidents. One objective of these procedures is to describe the various processes surrounding management, documentation and tracking of serious or minor adverse effects that may arise during and after a clinical trial with or without a research product. They also define any reporting requirements that apply to the developer, regulatory bodies and Research Ethics Committee (REC). All serious AEs will be reported punctually to the CHUM's Institutional Review Board. In the event of a SAE or UP, the PI implement the following procedures:

1. When the study coordinator and/or PI become aware of a serious AE, reporting must be implemented in a timely manner
2. The study coordinator will complete the required Quebec-government "Adverse Event Reporting Form" and submit the form to the PI.
3. The event will be reviewed to determine whether it is a SAE or an AE.
4. The serious AE form will then be submitted to the CHUM Institutional Review Board regarding these deadlines

3.7 Attendance and Withdrawal Criteria

Participants will be encouraged to attend all scheduled treatments. Those that do meet the following criteria will be excluded from the per protocol analysis if they:

(1) Miss / Fail to attend more than 2 treatment days in the course overall.
(2) Miss / Fail to attend more than 10 treatment sessions overall.
(3) Cannot tolerate stimulation
(4) Change their regimen of psychotropics during the treatment period.
(5) Withdraw consent to participate.

3.8 Clinical Trial Registration

This study is registered on www.clinicaltrials.gov. **NCT05194267**.

4.0 SUBJECT INCLUSION/EXCLUSION
4.1 Inclusion Criteria

4.1 Inclusion Criteria
Patients will be included if they:
(1) are outpatients
(2) are voluntary and competent to consent to treatment
(3) have a Mini-International Neuropsychiatric Interview (MINI) confirmed diagnosis of MDD, single or recurrent
(4) are between the ages of 18 and 65
(5) have a score ≥ 17 on the HRSD-17 item
(6) have had no increase or initiation of any psychotropic medication in the 4 weeks prior to screening
(7) able to adhere to the treatment schedule
(9) have normal blood work (thyroid, complete blood count, electrolytes)

4.2 Exclusion Criteria
Patients are excluded if they:

(1) have a Mini-International Neuropsychiatric Interview (MINI) confirmed diagnosis of substance dependence or abuse within the last 3 months
(2) have a concomitant major unstable medical illness, cardiac pacemaker or implanted medication pump
(3) have active suicidal intent
(4) are pregnant
(5) have a lifetime Mini-International Neuropsychiatric Interview (MINI) diagnosis of bipolar I or II disorder, schizophrenia, schizoaffective disorder, schizophreniform disorder, delusional disorder, or current psychotic symptoms
(6) have a MINI diagnosis of obsessive compulsive disorder, post-traumatic stress disorder (current or within the last year), anxiety disorder (generalized anxiety disorder, social anxiety disorder, panic disorder), or dysthymia, that is assessed by a study investigator to be primary and causing greater impairment than MDD
(7) have a diagnosis of any personality disorder, and assessed by a study investigator to be primary and causing greater impairment than MDD
(8) have failed a course of ECT in the current episode or previous episode
(9) have any significant neurological disorder or insult including, but not limited to: any condition likely to be associated with increased intracranial pressure, space occupying brain lesion, any history of seizure except those therapeutically induced by ECT or a febrile seizure of infancy, cerebral aneurysm, Parkinson's disease, Huntington's chorea, multiple sclerosis, significant head trauma with loss of consciousness for greater than 5 minutes
(10) have an intracranial implant (e.g., aneurysm clips, shunts, stimulators, cochlear implants, or electrodes) or any other metal object within or near the head, excluding the mouth, that cannot be safely removed
(11) if participating in psychotherapy, must have been in stable treatment for at least 3 months prior to entry into the study, with no anticipation of change in the frequency of therapeutic sessions, or the therapeutic focus over the duration of the study
(12) clinically significant laboratory abnormality, in the opinion of the one of the principal investigators or study physicians
(13) currently take more than lorazepam 2 mg daily (or equivalent) or any dose of an anticonvulsant due to the potential to limit rTMS efficacy
(14) non-correctable clinically significant sensory impairment (i.e., cannot hear well enough to cooperate with the interview)
(15) use of potentially irritant topical treatments (ex: retinoids, alpha hydroxy acids)
(16) esthetic procedure on scalp or face within the last 6 months (laser, fillers, surgery, botulinic toxin,etc)
(17) Active skin condition on face or scalp that would limit the application of the device or would unable the investigators to assess the skin following treatment

5.0 DATA MANAGEMENT

REDCap software will be used for data collection and overall study data management over the course of this project. REDCap is an open-source, web-based clinical data management and electronic data capture system and database. The system is developed and managed in compliance with HIPAA, PIPEDA, and FDA 21 CFR Part 11 regulations, providing functions such as defined user roles and privileges, user authentication and encryption, electronic signatures, de-identification of protected health information, comprehensive auditing features to record and monitor access and changes to data, and a validated software development lifecycle. This system will be used to design electronic case report forms (eCRFs), data entry, data monitoring and cleaning, and for the query and export of datasets for statistical analysis and predictive modeling.

6.0 CONSENT AND CONFIDENTIALITY

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. All patients referred by a general physician or psychiatrist will undergo an extensive consultation with a brain stimulation psychiatrist, who will explain the research study to the patient and answer any questions that may arise. Patients will then be seen for eligibility screening by qualified research personnel. Research personnel will explain the trial in detail prior to obtaining consent. Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting the study. Once consent is obtained according to REB and GCP/Tri-Council guidelines, the research personnel will confirm inclusion/exclusion criteria is met before proceeding with baseline testing. Patients will be informed that they can withdraw participation at any point during the study and the rights and welfare of the participants will be protected by emphasizing that the quality of the participant's medical care will not be adversely affected if they decline to participate in this study. A copy of the informed consent document will be given to the participants for their records.

The confidentiality of the data collected and identity of the individuals participating in this study will be strictly maintained. All files pertaining to subjects in the study will be coded numerically. Subject names will not be supplied to anyone not directly involved in the study conduct. For this research study, required personal health information include name, address, date of birth, new or existing medical records that includes psychiatric or medical conditions, current and past medications, presence of surgical implants, and illnesses or psychiatric procedures that may influence the ability to participate in the study. In addition, a health card number will also be required for patient registration. Some personal health information such as consultation reports, medical history and blood test results may be kept as source documents. This information will be obtained from the subject, his/her physician, or his/her medical health record. Source documents will always be kept in a locked filing cabinet to limit access, and in the case of electronic source documents, files will be password-protected and saved in a secure server. However, our case report forms (CRF's) will not contain any personal health information. Only the subject number will be recorded in the CRF, and if the subject name appears on any other document (e.g. laboratory report), it must be obliterated on the copy of the document retained in the Trial Master File or made available for audit. Study findings stored on a computer will be stored in accordance with data protection laws. Subjects will be informed that representatives of other parties (including pharmaceutical companies), ethics committee (IEC)/institutional review board (IRB) or regulatory authorities may inspect their records to verify the information collected, and that all personal information made available for inspection will be handled in the strictest confidence and in accordance with data protection laws. The investigator will maintain an encrypted and password protected personal subject identification list (subject numbers with the corresponding subject names) to enable records to be identified and retrieved.

7.0 TIMELINE

Fall 2021: Project submission to the research scientific and ethics boards
Winter 2022 to Summer 2023: Recruitment
Fall 2023: End of data collection, statistical analyses and redaction

8.0 IMPACT

If definite proof could be made that tDCS is effective for MDD, this would represent a major paradigm shift in the field. tDCS is a potentially highly scalable technology given its low-cost and

portability, and could revolutionize first-line MDD treatment; with patients having an alternative to medication. If our pilot project proves feasible, this could pave the way for a large-scale randomized controlled trial. Our tDCS approach could also be applied in other contexts, such as for relapse prevention after TMS, ketamine or ECT, as well as in other psychiatric pathologies (psychosis, bipolarity, obsessive-compulsive disorder).

References

1. Evaluation I of HM and. Global Health Data Exchange (GHDx) [Internet]. [cited 2021 Oct 19]. Available from: http://ghdx.healthdata.org/gbd-results-tool?params=gbd-api-2019-permalink/d780dffbe8a381b25e1416884959e88b

2. Gaynes BN, Warden D, Trivedi MH, Wisniewski SR, Fava M, Rush AJ. What Did STAR*D Teach Us? Results From a Large-Scale, Practical, Clinical Trial for Patients With Depression. Psychiatr Serv. 2009;60(11):1439–45.

3. Warden D, Rush AJ, Trivedi MH, Fava M, Wisniewski SR. The STAR*D project results: A comprehensive review of findings. Curr Psychiat Rep. 2007;9(6):449–59.

4. Mendlowitz AB, Shanbour A, Downar J, Vila-Rodriguez F, Daskalakis ZJ, Isaranuwatchai W, et al. Implementation of intermittent theta burst stimulation compared to conventional repetitive transcranial magnetic stimulation in patients with treatment resistant depression: A cost analysis. Plos One. 2019;14(9):e0222546.

5. Kennedy SH, Lam RW, McIntyre RS, Tourjman SV, Bhat V, Blier P, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder: Section 3. Pharmacological Treatments. Can J Psychiatry Revue Can De Psychiatrie [Internet]. 2016;61(9):540–60. Available from: http://journals.sagepub.com/doi/10.1177/0706743716659417

6. Negt P, Brakemeier E-L, Michalak J, Winter L, Bleich S, Kahl KG. The treatment of chronic depression with cognitive behavioral analysis system of psychotherapy: a systematic review and meta-analysis of randomized-controlled clinical trials. Brain Behav. 2016;6(8):e00486.

7. Antal A, Alekseichuk I, Bikson M, Brockmöller J, Brunoni AR, Chen R, et al. Low intensity transcranial electric stimulation: Safety, ethical, legal regulatory and application guidelines. Clin Neurophysiol. 2017;128(9):1774–809.

8. Bikson M, Grossman P, Thomas C, Zannou AL, Jiang J, Adnan T, et al. Safety of Transcranial Direct Current Stimulation: Evidence Based Update 2016. Brain Stimul. 2016;9(5):641–61.

9. Palm U, Kumpf U, Behler N, Wulf L, Kirsch B, Wörsching J, et al. Home Use, Remotely Supervised, and Remotely Controlled Transcranial Direct Current Stimulation: A Systematic Review of the Available Evidence: REMOTELY CONTROLLED tDCS. Neuromodulation Technology Neural Interface. 2017;21(4):323–33.

10. Lefaucheur J-P, Antal A, Ayache SS, Benninger DH, Brunelin J, Cogiamanian F, et al. Evidence-based guidelines on the therapeutic use of transcranial direct current stimulation (tDCS). Clin Neurophysiol. 2017;128(1):56–92.

11. Razza LB, Palumbo P, Moffa AH, Carvalho AF, Solmi M, Loo CK, et al. A systematic review and meta-analysis on the effects of transcranial direct current stimulation in depressive episodes. Depress Anxiety. 2020;37(7):594–608.

12. Nitsche MA, Cohen LG, Wassermann EM, Priori A, Lang N, Antal A, et al. Transcranial direct current stimulation: State of the art 2008. Brain Stimul. 2008;1(3):206–23.

13. Im JJ, Jeong H, Bikson M, Woods AJ, Unal G, Oh JK, et al. Effects of 6-month at-home transcranial direct current stimulation on cognition and cerebral glucose metabolism in Alzheimer's disease. Brain Stimul. 2019;12(5):1222–8.

14. Brunoni AR, Moffa AH, Sampaio-Junior B, Borrione L, Moreno ML, Fernandes RA, et al. Trial of Electrical Direct-Current Therapy versus Escitalopram for Depression. New Engl J Medicine. 2017;376(26):2523–33.

15. Brunoni AR, Valiengo L, Baccaro A, Zanão TA, Oliveira JF de, Goulart A, et al. The Sertraline vs Electrical Current Therapy for Treating Depression Clinical Study: Results From a Factorial, Randomized, Controlled Trial. Jama Psychiat. 2013;70(4):383–91.

16. Agboada D, Mosayebi-Samani M, Kuo M-F, Nitsche MA. Induction of long-term potentiation-like plasticity in the primary motor cortex with repeated anodal transcranial direct current stimulation – Better effects with intensified protocols? Brain Stimul. 2020;13(4):987–97.

17. Miron J-P, Voetterl H, Fox L, Hyde M, Mansouri F, Dees S, et al. Optimized repetitive transcranial magnetic stimulation techniques for the treatment of major depression: A proof of concept study. Psychiat Res. 2021;298:113790.

18. Miron J-P, Hyde M, Fox L, Sheen J, Voetterl H, Mansouri F, et al. Evaluation of a 5 day accelerated 1 Hz repetitive transcranial magnetic stimulation protocol in major depression: A feasibility study. J Affect Disord Reports. 2021;4:100077.

19. Rodríguez N, Opisso E, Pascual-Leone Á, Soler MD. Skin Lesions Induced by Transcranial Direct Current Stimulation (tDCS). Brain Stimul. 2014;7(5):765–7.

20. Pilloni G, Woods AJ, Charvet L. No risk of skin lesion or burn with transcranial direct current stimulation (tDCS) using standardized protocols. Brain Stimul. 2021;14(3):511–2.

21. Mondino M, Poulet E, Brunelin J. Moving to accelerated protocols of tDCS in schizophrenia: A case report. Brain Stimul. 2021;14(4):822–4.

22. Cole EJ, Stimpson KH, Bentzley BS, Gulser M, Cherian K, Tischler C, et al. Stanford Accelerated Intelligent Neuromodulation Therapy for Treatment-Resistant Depression. Am J Psychiat. 2020;177(8):716–26.

23. Julious SA. Issues with number needed to treat. Stat Med. 2005;24(20):3233–5.

24. Browne RH. On the use of a pilot sample for sample size determination. Stat Med. 1995;14(17):1933–40.

25. Hertzog MA. Considerations in determining sample size for pilot studies. Res Nurs Health. 2008;31(2):180–91.

26. Johanson GA, Brooks GP. Initial Scale Development: Sample Size for Pilot Studies. Educ Psychol Meas. 2010;70(3):394–400.

27. Cocks K, Torgerson DJ. Sample size calculations for pilot randomized trials: a confidence interval approach. J Clin Epidemiol. 2013;66(2):197–201.

28. Julious SA, Owen RJ. Sample size calculations for clinical studies allowing for uncertainty about the variance. Pharm Stat. 2006;5(1):29–37.

29. Whitehead AL, Julious SA, Cooper CL, Campbell MJ. Estimating the sample size for a pilot randomised trial to minimise the overall trial sample size for the external pilot and main trial for a continuous outcome variable. Stat Methods Med Res. 2016;25(3):1057–73.

30. Slotema CW, Blom JD, Hoek HW, Sommer IEC. Should we expand the toolbox of psychiatric treatment methods to include Repetitive Transcranial Magnetic Stimulation (rTMS)? A meta-analysis of the efficacy of rTMS in psychiatric disorders. J Clin Psychiatry. 2010;71(7):873–84.

31. Brunoni AR, Amadera J, Berbel B, Volz MS, Rizzerio BG, Fregni F. A systematic review on reporting and assessment of adverse effects associated with transcranial direct current stimulation. Int J Neuropsychoph. 2011;14(8):1133–45.