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Original Protocol

(Original translated version as submitted to the Ethics Committee of the University Hospital of the University of São Paulo, Brazil, on May 16th, 2019)

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PSYLECT PROJECT: PSYCHOLOGICAL INTERVENTIONS AND TRANSCRANIAL DIRECT CURRENT STIMULATION FOR DEPRESSION

a. Theme:

The subject of this study is the association of a non-invasive neuromodulation technique in a home setting, transcranial direct current stimulation (tDCS), with a smartphone-based behavioral therapy (SBT) protocol, in the treatment of unipolar depression in adult patients.

b. Objective:

The aim is to study the combined effect of home-based tDCS associated with SBT, compared to double placebo, in adult patients with unipolar depression, without concomitant use of antidepressant medications, during an initial period of 6 weeks.

c. Social relevance:

c.1 Depression

In the United Nations' Sustainable Development Goals for 2030, it was established that mental health is a global priority, emphasizing the crucial need to reduce the prevalence, morbidity, and premature mortality associated with mental disorders[1]. Data from the Global Burden of Disease Study shows that mental disorders account for 10.4% of years lived with disability (YLDs) and up to 28.5% of disability-adjusted life years (DALYs), among all diseases[2]. In Brazil, mental disorders account for 9.5% of all DALYs and rank third and first in terms of YLDs and DALYs, respectively. [3]. Among mental disorders, depression is the third most important cause of YLD worldwide. Global data shows a one-year prevalence of depression at 6.6% and a lifetime prevalence of 16.2% [4]. The main comorbidities found in depression, such as pain syndromes, anxiety disorders, and alcohol dependence, also rank among the 25 most important causes of disability[2]. Depression has a high morbidity because it typically begins in early adulthood, with a peak occurring in the second and third decades of life[5], and presents a chronic course with recurrent episodes[6]. More alarmingly, the suicide rate is approximately 15% in severe depressive episodes[7].

At the present time, response and remission rates in depression are only moderate. Data from STAR*D, a large and pragmatic multicenter clinical trial, show that less than 1/3 of patients achieve remission after the first antidepressant treatment, and up to 1/3 of depressed patients do not achieve remission after four or more adequate antidepressant treatments[8]. In addition, pharmacotherapy carries a significant risk of adverse effects, particularly at high doses[9], without substantial differences in efficacy[10]. This finding highlights that the current treatment for depression is based on a "trial and error" paradigm and therefore can take weeks or even months to figure out the optimal antidepressant treatment for a specific patient. Psychotherapeutic modalities, in turn, have moderate efficacy in the treatment of depression and fewer adverse effects than pharmacotherapy[11]. However, psychotherapeutic modalities present issues such as the limited global availability of properly trained therapists, the need for active participation and patient engagement, and a longer time for the onset of therapeutic benefits[12].

c.2 Transcranial direct current stimulation (tDCS)

Non-invasive brain stimulation (NIBS) techniques do not require surgery and are less invasive, less focal, and more tolerable than implantable techniques, such as *deep brain stimulation* (DBS) and vagus nerve stimulation (VNS)[13]. NIBS techniques include transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), which use magnetic and/or electric fields, respectively, to promote changes in cortical excitability[14]. These approaches do not require sedation or anesthesia, and evidence indicates that

they have excellent safety and tolerability profile[15,16]. For tDCS, additional advantages include its accessibility, ease of use, and portability[14].

In an initial meta-analysis (n=289), we demonstrated that active tDCS is superior to simulated tDCS in relation to response, remission, and other outcomes of improvement in depression[17]. A recent and updated meta-analysis (n=446) confirmed our findings[18]. Due to its portability and ease of use, tDCS has been investigated as a potentiating and substitutive treatment for antidepressant drugs. In the Sertraline *versus Electric Current Therapy for Treating Depression Clinical Study* - SELECT-TDCS (FAPESP grant 09/05728-7), we recruited 120 depressed patients without antidepressants, who were randomized into four groups (2x2 factorial design): placebo (SELECT-sham), sertraline alone (SELECT-SSRI), tDCS alone (SELECT-tDCS) and combined therapy (SELECT – Combined therapy)[19]. We showed that the combined treatment was significantly more effective than each treatment alone, although the findings that tDCS and sertraline were not different were limited, since the dose of the drug was at the lower limit of the efficacy range and the study was not *a priori* designed to assess non-inferiority[19]. In SELECT-TDCS, the heterogeneity of the treatment may have been due to different dosages of electric current in the brain regions of interest, which was not measured in the study[20].

In the clinical trial *Escitalopram vs. Electric Current Therapy to Treat Depression Clinical Study (*ELECT-TDCS) (FAPESP grant 12 / 20911-5), we compared tDCS versus escitalopram 20mg/day (maximum dose recommended by the FDA)[21]. The margin of non-inferiority was established as 50% of the efficacy of escitalopram in relation to placebo[21]. ELECT-TDCS lasted longer than SELECT-TDCS (10 weeks instead of 6), applied more tDCS sessions (22 instead of 12) and recruited 245 participants[21]. The primary outcome did not reveal non-inferiority of tDCS vs. escitalopram[21]. Superiority analyses revealed superiority of tDCS in relation to placebo[21]. In this sense, the antidepressant effects of tDCS to date have been modest and heterogeneous.

Generally speaking, tDCS is not yet considered a conventional treatment for depression, since its effects are modest and heterogeneous. In addition, access to tDCS is still limited; For example, home-use tDCS devices are not fully developed, and daily sessions for several weeks in the clinic are impractical for those living in remote areas. **Therefore, despite significant advances, there is an urgent need to increase the efficacy and clinical usability of tDCS**.

c.3 Smartphone-based behavioral therapy (SBT)

Remotely administered cognitive-behavioral therapy is a modality of self-directed psychotherapy, which has been employed in the treatment of depression for the past 30 years, according to available technology (books, phone, computer, text messages, and more recently, smartphone apps). A pilot study in 1990 demonstrated that face-to-face CBT versus the computer-administered version were equally effective[22]. The computerized programs were usually carried out in interactive modules composed of various multimedia techniques to favor the engagement and motivation of patients, such as photos, advice, sketches, and videos. Although these therapies initially offered therapist support among modules [23], they eventually evolved into fully computerized modules without support[24]. Currently, the evidence map for technology-based treatments is broad, including diverse levels of automation, technologies and interventions[25].

In a recent review to evaluate the effectiveness of mental interventions based on smartphone use, Firth *et al*. included 18 randomized controlled trials (RCTs)[26]. The nature of the interventions was heterogeneous, including cognitive training, mood self-monitoring, mindfulness, psychoeducation, behavioral activation, cognitive behavioral therapy-based techniques, and cognitive bias modification. The authors identified a moderate overall effect size (g=0.38), which was smaller (g=0.22) in studies that compared the intervention with respect to the "active" control. A trend of larger effect sizes was observed for fully automated applications (e.g., those that do not involve a human) and for applications that provide feedback (e.g., statistics and progress). Despite the smaller effect sizes in trials that used only cognitive training, the nature of the intervention did not influence the effect sizes. **The nature of our SBT intervention involves an electronic avatar that offers advice, feedback, and educational information about depressive symptoms, as well as behavioral strategies for dealing with them.**

d. Objectives:

In the Psylect study, the primary endpoint will be the use of home-use tDCS associated with smartphone app-based behavioral therapy (SBT), versus double placebo, in primary and secondary care patients with unipolar depression. Our main hypothesis is that the combined treatment is superior to the double placebo in reducing depressive symptoms over a 6-week treatment protocol.

In this sense, we consider that tDCS potentiates the effects of a concomitantly administered psychotherapeutic intervention (in this case, SBT), since tDCS, through changes promoted in the neuronal membrane potential, is particularly effective in increasing the excitability of neuronal networks pre-activated by cognitive activities[27].

In depression, two small clinical trials (pilot studies) evaluated the antidepressant effects of tDCS associated with cognitive control therapy (CCT, a cognitive intervention that engages the left dorsolateral prefrontal cortex [CPFDLE] via voluntary attention and working memory tasks), showing some benefit of combination therapy in exploratory outcomes[28,29]. Additionally, a large multicenter study (n=192), still running, is evaluating the efficacy of tDCS combined with cognitive behavioral therapy (CBT) in group[30]. Promising results were also found in relation to the combination of tDCS with CBT or with modification of attentional bias, in schizophrenia and anxiety, respectively[31].

Probably, tDCS and cognitive-behavioral therapy (CBT) have synergistic effects. Self-referential thinking and pessimistic ruminations are characteristic of depression and are associated with network hyperactivity between the anterior cingulate cortex (ACC) and the prefrontal cortex (PFC)[32]. CBT is aimed at neutralizing the negative self-bias characteristic of depression and has been associated with decreased functional connectivity between these brain regions throughout symptomatic improvement[33]. In a study involving individuals with anxiety disorder, tDCS on the PFC reduced the level of reactivity to threats of the amygdala, increased frontal activity, and improved behavioral outcomes[34]. Therefore, as the two interventions (psychotherapy and tDCS) target the PFC, we assume that, when both are applied concomitantly, tDCS can improve neural activity in brain areas recruited during the psychotherapeutic process[35], through synergistic action.

In fact, even if the therapies do not interact, it may also be advantageous to combine them, aiming at the additive effects, considering that tDCS in depression is usually applied 20-30 minutes a day, for several days, and produces minimal side effects that do not distract or demotivate the patient. Previous studies involving tDCS[36] instructed patients to remain "at rest" during the session. Although this variable has not yet been addressed, the state at "at rest" is problematic because it favors wandering, which in depressive patients can aggravate anxiety and rumination[37]. From a clinical perspective, the combination of psychological interventions during tDCS sessions is feasible and can leverage both interventions.

We propose, then, the evaluation of the efficacy of home use of tDCS combined with a behavioral therapy, through a smartphone application (SBT). This approach is particularly interesting because it circumvents the issue of geographical displacement, reduces the overall costs of interventions and travel to treatment sites. In fact, forms of ACT are already standardized[38].

Secondary endpoints of Psylect include examination for: (1) secondary depression scales; (2) clinical response and remission scales; (3) clinical predictors of response; (4) tolerability; (5) cognitive outcomes and (6) clinical usability of tDCS at home.

We expect the experimental intervention to be superior to the control. For item (4), we expect that experimental and control groups will present similar rates of adverse events. For item (6), we expect that > 80% of the participants will evaluate the use of tDCS for home use as (very) easy.

After the randomized phase, patients will be asked to enter an open-label follow-up phase of up to 6 months, to see if clinical and cognitive gains will be maintained for a longer period.

e. Study setting:

University Hospital of the University of São Paulo – HU/USP (screening and clinical evaluations) and patients' homes (tDCS+SBT sessions).

f. Study population:

Population of patients of both sexes, aged 18 to 59 years, without distinction of color/race and/or ethnicity, without distinction of sexual orientation and/or gender identity, without distinction of class or social group, with eight or more years of schooling, access to smartphone *and* personal internet connection, **diagnosed with unipolar depression and requiring primary or secondary care by the Brazilian Unified Health System (SUS)**. We hope to introduce 210 patients to our research. Only patients with the capacity to make their own decisions will be accepted in the research, without changes in judgment of reality of any etiology.

g. Ethical guarantees for study participants:

The research will be carried out by a team of trained physicians and psychologists, based at the University Hospital of the University of São Paulo (HU-USP). The triage of patients will be performed by this team, at the HU-USP, and the clinical information will be collected under medical secrecy. Patients will always be properly oriented about all scientific and ethical aspects of research, in accessible language and adaptable to their biopsychosocial reality. Patients will only be included in the research by signing a free and informed consent form and will keep a copy of the signed document in their possession.

h. Methods:

For the application of the tDCS sessions, we will use portable Flow devices (Flow™ Neuroscience, Malmö, Sweden) **Figure 1**. The anode and cathode will be positioned over the left and right DLPFC, respectively. We will use a current of 2mA on a circular surface of 22.9 cm^2 (current density = 0.09mA/cm^2), for 30 minutes, using customized and salinized pre-humidified sponges. Fifteen tDCS sessions will be held five times a week for the first three weeks, and two sessions per week until week 6 (totaling 21 sessions). The SBT intervention will be performed through the Flow **-** Depression app (iOS or Android) developed by Flow™, which uses several behavioral therapy modules. For each session, a different module is offered, encompassing six main types: nutrition (3 sessions), meditation (4 sessions), physical exercise (3), sleep hygiene (4), relapse prevention (4) and behavioral activation (4). In addition, there will be an introductory session and a final session (excerpts from these modules are shown in "Appendix 1").

Figure **1** shows a Flow™ device designed for home use. The figure on the left shows the device and smartphone app that controls, via Bluetooth, the tDCS and SBT sessions. The device is charged via a Micro 2.0 connector. The figure on the right shows the device placed over a phantom head. The anode and cathode are placed without difficulty on the left and right prefrontal cortex, respectively. The correct position in terms of angulation and distance to the eyebrows is achieved using an augmented reality feature of the app and the front camera of the smartphone.

The SBT appl uses an interactive format, offering advice, *feedback* and explanatory videos generated from the avatar of the virtual therapist, according to the responses of the participants. Although the duration of the session may vary according to the patient's response and how quickly they interact with the avatar, it is designed to coincide with the duration of the tDCS session (i.e., 30 minutes).

Each module features content to promote health, well-being and/or improve depressive symptoms. For example, healthy dietary practices reduce the risk of developing depression[39]. Physical exercises[40] and meditation[41] can help restore psychological balance. Behavioral activation is a strategy employed for subliminal depression [42] and sleep hygiene helps with insomnia, which is an important symptom in depression[43].

There are different options for sham SBT that can be divided into "active" interventions (general health guidelines, *links* to *websites* that offer counseling for individuals with depression) or "inactive" interventions (no intervention or waiting list). In *Psylect*, we will employ "active simulated SBT," consisting of the use of neutral, non-targeted electronic content, such as information about daily news and variety and videos, and images with random content. Patients will install and use the same app, but the code entered when the app is launched will redirect them to "simulated mode," offering a mix of information and videos from Brazilian portals and YouTube channels.

The recruitment will take place from referrals by a team of health professionals from the HU-USP and also from the Hospital das Clínicas of the Medical School of USP, as well as self-referrals through advertisements in search engines on the internet and social networks.

i. Schedule:

Step Identification	Beginning	Term
Screening of participants	February 3, 2020	August 2, 2021
Double-blind and randomized phase	February 3, 2020	September 10, 2021
Open follow-up phase	March 16, 2020	February 18, 2022
Analysis of data from the randomized phase	September 13, 2021	December 13, 2021
Open phase data analysis	February 22, 2022	May 23, 2022

We offer assurance that the Psylect study will only be initiated from the approval by the CEP-CONEP (Ethical Review Board) System of the University Hospital of the University of São Paulo (USP).

j. Inclusion and exclusion criteria of study participants:

The diagnosis of depression will be made by trained psychiatrists/psychologists, according to the DSM-5 criteria and using the Portuguese version of the Structured Clinical Interview for the DSM-5 (SCID-5). All patients should present a **diagnosis of a major depressive episode** and understand and sign the informed consent form.

The **inclusion criteria** are: (a) age between 18 and 59 years; (b) initial score on the Hamilton scale, 17 items (HAMD17) ≥ 17 at the time of screening and initial evaluation; (c) at least 8 years of schooling; (d) availability to use smartphone applications (i.e., having a smartphone with internet access).

Exclusion **criteria** are: (a) previous episodes of mania/hypomania or diagnosis of bipolar disorder; (b) contraindications to the use of tDCS, such as metal plates on the head; (c) suicidal ideation with planning, or attempted suicide in the last 4 weeks prior to study enrollment; (d) refractoriness to more than 3 treatments with antidepressant drugs; (e) pregnancy; (f) other psychiatric diagnoses, such as schizophrenia, substance dependence, personality disorders, among others (anxiety disorders as a comorbidity will be included); (g) severe clinical and neurological conditions; (h) depressive symptoms better explained by other clinical conditions (hypothyroidism, anemia, etc.) or by other psychiatric disorders.

Participants using antidepressant medications will undergo a *washout* period of 5 half-lives prior to study entry (5 weeks in the case of fluoxetine). Those using benzodiazepines will be included up to a maximum dose of diazepam equivalent to 10 mg/day. Other psychotropic medications will not be discontinued if they are being used for other reasons, rather than mood treatment, and in low doses.

k. Risks and benefits involved in the execution of the study:

Minimal risk. The two procedures (tDCS and SBT) have already been studied in isolation in the home environment and there are no reports of serious complications or risk of brain damage. Regarding tDCS, the current is of low intensity and safe for use in depression. The most reported side effects are a tingling sensation in the scalp[44], minimized through humidification of the electrodes with saline. The risk of hypomanic switch exists, but it is small and similar in active tDCS versus placebo[45].

The main benefit for the patients involved will be the possible improvement in depressive symptoms, with the possibility of participation in a follow-up phase with a total duration of 6 months, where the two treatments (tDCS + SBT) will be offered in an open phase.

The research will be conducted in a home setting, but patients will be expected to come to the research center for periodic clinical evaluations and will also have remote access to research team members to ask questions and share their experiences with the Flow equipment. Patients with clinical or psychiatric complications will be referred to and treated at the University Hospital of University of São Paulo, and will receive cost-free treatment according to the level of complexity required. At the end of the research, the participants will be referred to their outpatient clinics/treatment level of origin, with all the necessary orientations and prescriptions.

l. Study discontinuation criteria:

The researchers have the prerogative to cease study participation in case of the emergence of any clinical or psychiatric complication that puts the patient's health and/or life at risk. In the specific case of *Psylect*, we will pay special attention to the emergence of suicidal ideation and/or planning and (hypo)manic switch. In these cases, the participant will be excluded from the research, regardless of the time of onset, and referred for appropriate treatment.

m. Study results:

We offer assurance that the results of the study will be disseminated to the whole society, in appropriate vehicles for the scientific community and the participating patients, explaining that the research was carried out from the University Hospital of USP.

n. Dissemination of results:

We offer guarantee that the results of our research will be forwarded for publication, with all due credit to the authors involved.

o. References:

1. Izutsu T, Tsutsumi A, Minas H, Thornicroft G, Patel V, Ito A. Mental health and wellbeing in the Sustainable Development Goals. Lancet Psychiatry 2015;2:1052-4.
2. DALYs GBD, Collaborators H. Global, regional, and national disability-adjusted life-years (DALYs) for 315 diseases and injuries and healthy life expectancy (HALE), 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet 2016;388:1603-58.
3. Bonadiman CSC, Passos VMA, Mooney M, Naghavi M, Melo APS. The Burden of disease attributable to mental and substance use disorders in Brazil: Global Burden of Disease Study, 1990 and 2015. Rev Bras Epidemiol 2017;20Suppl 01:191-204.
4. Kupfer DJ, Frank E, Phillips ML. Major depressive disorder: new clinical, neurobiological, and treatment perspectives. Lancet 2012;379:1045-55.
5. Kessler RC, Birnbaum H, Bromet E, Hwang I, Sampson N, Shahly V. Age differences in major depression: results from the National Comorbidity Survey Replication (NCS-R). Psychol Med 2010;40:225-37.
6. Kessler RC, Berglund P, Demler O, et al. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). JAMA 2003;289:3095-105.
7. Chachamovich E, Stefanello S, Botega N, Turecki G. [Which are the recent clinical findings regarding the association between depression and suicide?]. Braz J Psychiatry 2009;31 Suppl 1:S18-25.
8. Rush AJ, Trivedi MH, Wisniewski SR, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Am J Psychiatry 2006;163:1905-17.
9. Anderson IM, Ferrier IN, Baldwin RC, et al. Evidence-based guidelines for treating depressive disorders with antidepressants: a revision of the 2000 British Association for Psychopharmacology guidelines. J Psychopharmacol 2008;22:343-96.
10. Trivedi MH, Fava M, Wisniewski SR, et al. Medication augmentation after the failure of SSRIs for depression. N Engl J Med 2006;354:1243-52.
11. Cuijpers P, Geraedts AS, van Oppen P, Andersson G, Markowitz JC, van Straten A. Interpersonal psychotherapy for depression: a meta-analysis. Am J Psychiatry 2011;168:581-92.
12. Keller MB, McCullough JP, Klein DN, et al. A comparison of nefazodone, the cognitive behavioral-analysis system of psychotherapy, and their combination for the treatment of chronic depression. N Engl J Med 2000;342:1462-70.
13. Klooster DC, de Louw AJ, Aldenkamp AP, et al. Technical aspects of neurostimulation: Focus on equipment, electric field modeling, and stimulation protocols. Neurosci Biobehav Rev 2016;65:113-41.
14. Brunoni AR, Sampaio-Junior B, Moffa AH, et al. Noninvasive brain stimulation in psychiatric disorders: a primer. Braz J Psychiatry 2019;41:70-81.
15. Rossi S, Hallett M, Rossini PM, Pascual-Leone A, Safety of TMSCG. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clin Neurophysiol 2009;120:2008-39.
16. Bikson M, Grossman P, Thomas C, et al. Safety of Transcranial Direct Current Stimulation: Evidence Based Update 2016. Brain Stimul 2016;9:641-61.
17. Brunoni AR, Moffa AH, Fregni F, et al. Transcranial direct current stimulation for acute major depressive episodes: meta-analysis of individual patient data. Br J Psychiatry 2016;208:522-31.
18. Mutz J, Edgcumbe DR, Brunoni AR, Fu CHY. Efficacy and acceptability of non-invasive brain stimulation for the treatment of adult unipolar and bipolar depression: A systematic review and meta-analysis of randomised sham-controlled trials. Neurosci Biobehav Rev 2018;92:291-303.
19. Brunoni AR, Valiengo L, Baccaro A, et al. The sertraline vs. electrical current therapy for treating depression clinical study: results from a factorial, randomized, controlled trial. JAMA Psychiatry 2013;70:383-91.
20. Lisanby SH. Noninvasive Brain Stimulation for Depression - The Devil Is in the Dosing. N Engl J Med 2017;376:2593-4.
21. Brunoni AR, Moffa AH, Sampaio-Junior B, et al. Trial of Electrical Direct-Current Therapy versus Escitalopram for Depression. N Engl J Med 2017;376:2523-33.
22. Selmi PM, Klein MH, Greist JH, Sorrell SP, Erdman HP. Computer-administered cognitive-behavioral therapy for depression. Am J Psychiatry 1990;147:51-6.
23. Proudfoot J, Goldberg D, Mann A, Everitt B, Marks I, Gray JA. Computerized, interactive, multimedia cognitive-behavioural program for anxiety and depression in general practice. Psychol Med 2003;33:217-27.
24. de Graaf LE, Gerhards SA, Arntz A, et al. Clinical effectiveness of online computerised cognitive-behavioural therapy without support for depression in primary care: randomised trial. Br J Psychiatry 2009;195:73-80.

25. Apaydin EA, Maher AR, Raaen L, et al. The Use of Technology in the Clinical Care of Depression: An Evidence Map. J Clin Psychiatry 2018;79.
26. Firth J, Torous J, Nicholas J, et al. The efficacy of smartphone-based mental health interventions for depressive symptoms: a meta-analysis of randomized controlled trials. World Psychiatry 2017;16:287-98.
27. Jackson MP, Rahman A, Lafon B, et al. Animal models of transcranial direct current stimulation: Methods and mechanisms. Clin Neurophysiol 2016;127:3425-54.
28. Segrave RA, Arnold S, Hoy K, Fitzgerald PB. Concurrent cognitive control training augments the antidepressant efficacy of tDCS: a pilot study. Brain Stimul 2014;7:325-31.
29. Brunoni AR, Boggio PS, De Raedt R, et al. Cognitive control therapy and transcranial direct current stimulation for depression: a randomized, double-blinded, controlled trial. J Affect Disord 2014;162:43-9.
30. Bajbouj M, Aust S, Spies J, et al. PsychotherapyPlus: augmentation of cognitive behavioral therapy (CBT) with prefrontal transcranial direct current stimulation (tDCS) in major depressive disorder-study design and methodology of a multicenter double-blind randomized placebo-controlled trial. Eur Arch Psychiatry Clin Neurosci 2018;268:797-808.
31. Sathappan AV, Luber BM, Lisanby SH. The Dynamic Duo: Combining noninvasive brain stimulation with cognitive interventions. Prog Neuropsychopharmacol Biol Psychiatry 2019;89:347-60.
32. Williams LM. Precision psychiatry: a neural circuit taxonomy for depression and anxiety. Lancet Psychiatry 2016;3:472-80.
33. Yoshimura S, Okamoto Y, Onoda K, et al. Cognitive behavioral therapy for depression changes medial prefrontal and ventral anterior cingulate cortex activity associated with self-referential processing. Soc Cogn Affect Neurosci 2014;9:487-93.
34. Ironside M, Browning M, Ansari TL, et al. Effect of Prefrontal Cortex Stimulation on Regulation of Amygdala Response to Threat in Individuals With Trait Anxiety: A Randomized Clinical Trial. JAMA Psychiatry 2018.
35. Bajbouj M, Padberg F. A perfect match: noninvasive brain stimulation and psychotherapy. Eur Arch Psychiatry Clin Neurosci 2014;264 Suppl 1:S27-33.
36. Borrione L, Moffa AH, Martin D, Loo CK, Brunoni AR. Transcranial Direct Current Stimulation in the Acute Depressive Episode: A Systematic Review of Current Knowledge. J ECT 2018;34:153-63.
37. Marchetti I, Koster EHW, Klinger E, Alloy LB. Spontaneous Thought and Vulnerability to Mood Disorders: The Dark Side of the Wandering Mind. Clin Psychol Sci 2016;4:835-57.
38. Gratzer D, Khalid-Khan F. Internet-delivered cognitive behavioural therapy in the treatment of psychiatric illness. CMAJ 2016;188:263-72.
39. Opie RS, Itsiopoulos C, Parletta N, et al. Dietary recommendations for the prevention of depression. Nutr Neurosci 2017;20:161-71.
40. Sarris J, O'Neil A, Coulson CE, Schweitzer I, Berk M. Lifestyle medicine for depression. BMC Psychiatry 2014;14:107.
41. Hofmann SG, Sawyer AT, Witt AA, Oh D. The effect of mindfulness-based therapy on anxiety and depression: A meta-analytic review. J Consult Clin Psychol 2010;78:169-83.
42. Mori A, Okamoto Y, Okada G, et al. Behavioral activation can normalize neural hypoactivation in subthreshold depression during a monetary incentive delay task. J Affect Disord 2016;189:254-62.
43. Maness DL, Khan M. Nonpharmacologic Management of Chronic Insomnia. Am Fam Physician 2015;92:1058-64.
44. Aparicio LVM, Guarienti F, Razza LB, Carvalho AF, Fregni F, Brunoni AR. A Systematic Review on the Acceptability and Tolerability of Transcranial Direct Current Stimulation Treatment in Neuropsychiatry Trials. Brain Stimul 2016;9:671-81.
45. Brunoni AR, Moffa AH, Sampaio-Junior B, Galvez V, Loo CK. Treatment-emergent mania/hypomania during antidepressant treatment with transcranial direct current stimulation (tDCS): A systematic review and meta-analysis. Brain Stimul 2017;10:260-2.

Final Protocol

Title: The Portable Transcranial Electrical Stimulation and Internet-Based Behavioral Therapy for Major Depression Study

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1. Introduction

Major depressive disorder (MDD) remains a leading cause of disability-adjusted life years (DALYs), despite traditional pharmacological and psychotherapeutic options [1]. MDD still affects more than 300 million people worldwide, with a chronic and recurrent course [2]. First-line treatments for MDD present significant caveats, as antidepressant medications are associated with modest efficacy [3] and adverse effects [4], while in-person cognitive-behavioral therapy (CBT) lacks wide-range availability, and involves higher costs and logistical burdens [5].

Transcranial direct current stimulation (tDCS), the most widely studied format of transcranial electrical stimulation (tES), is a non-invasive brain stimulation technique with moderate effectiveness for the treatment of MDD [6–9]. tDCS delivers continuous and weak electrical currents to the brain, thereby rebalancing neuronal activity and connectivity [10]. According to the neurobiology of MDD, tDCS trials for this condition commonly apply the anode over the left dorsolateral prefrontal cortex (DLPFC) and the cathode over the right DLPFC [6,9,11,12]. The DLPFC is associated with working memory, self-regulation, and decision making, and has been shown to be hypoactive in depression,

particularly in the left hemisphere [13]. This leads to a corresponding hyperactivity in the default-mode network, which has been linked with the self-referential and pessimistic ruminations observed in depressive disorders [14,15].

In the past 15 years, several trials showed that tDCS is moderately effective for MDD, suggesting that it could be a first-line intervention, especially in patients with a low-drug resistance [6,9]. However, such an approach is hampered by the limited scalability of tDCS treatment. The relative scarcity of skilled personnel and the logistical burdens and transportation costs associated with daily visits to external facilities are probably associated with its suboptimal utilization in clinical practice. In this context, recent technological advancements are progressively allowing tDCS to be performed remotely, and operated by patients themselves, therefore reducing costs and enhancing scalability. Although this approach sounds appealing, data from home-based trials are still preliminary. A recent open-label pilot study (n = 34) [16] and case series (n = 5) [17] have suggested that home-use tDCS is a feasible intervention for MDD, following necessary precautions and safety guidelines [18]. Furthermore, these studies were open-label and did not present a control arm, limiting the interpretation of their findings.

Concomitantly to these nascent advancements in the practice of home-based tDCS, growing attention has also been directed towards the combination of tDCS and neurobehavioral or psychotherapeutic interventions, aiming to engage the same brain regions of interest, and ultimately, achieve an additive or synergistic therapeutic effect [19,20]. For instance, two pilot, randomized, sham-controlled, clinical trials (RCTs), combining tDCS and cognitive-control training (CCT) for the treatment of MDD, have demonstrated positive, but preliminary results [21,22]. These studies applied a neurobehavioral intervention with tDCS and were performed at research centers.

However, both neurobehavioral and psychotherapeutic interventions can also be delivered remotely, in an internet-based and self-directed manner, especially using interactive smartphone apps [23]. A randomized clinical trial compared an app-based mental health intervention to a clinic-based group intervention, in patients with serious mental disorders, and found higher engagement and acceptability with the app-based intervention, and with similar clinical outcomes [24]. Meta-analyses that evaluated the effect of app-based interventions in MDD found superiority of these interventions over control conditions, with small to large effect sizes [23,25,26], and higher retention rates when there was human feedback and mood assessments through the apps [27].

Moreover, the recent research interest in mental health apps for the treatment of MDD is occurring within a larger framework encompassing the rapid development of digital mental health technologies, in great part, boosted by the social distancing restrictions imposed by the COVID-19 pandemic [28,29]. Therefore, the expansion of digital mental health interventions and their good usability enables better access to healthcare, cost reduction, personalized approaches, and adherence to treatment. While a few studies evaluating the combination of tDCS with CCT have been performed in research facilities, to the best of our knowledge, no controlled trial has investigated the synchronous combination of portable transcranial electrical stimulation (ptES) and a remotely delivered, self-directed and internet-based behavioral intervention (iBT), for the treatment of MDD, in adult patients.

Here, we describe the rationale, study design and methodology of the ongoing *Portable Transcranial Electrical Stimulation and Internet-based Behavioral Therapy for Major Depression Study* (PSYLECT). The main objective of this multi-arm, randomized, double-blind and sham-controlled clinical trial using digital features is to evaluate the efficacy, safety, tolerability, and usability of a combined and synchronous regimen of

active ptES and active iBT, as compared with active ptES in monotherapy, and a double-sham regimen, for the treatment of adult patients with MDD.

2. Patients and Methods

2.1 Overview

The PSYLECT trial consists of a randomized, double-blind, sham-controlled clinical trial, in which patients are allocated to one of 3 parallel arms: (1) active ptES + active iBT ("double active"); (2) active ptES + sham iBT ("ptES-only"); (3) sham ptES + sham iBT ("double-sham"). This study was approved by the Ethics Committees of the University Hospital (*Hospital Universitário - HU*) and Clinics Hospital (*Hospital das Clínicas - HC*) of the University of São Paulo, Brazil (CAAE: 13922419.1.0000.0076), according to the principles stated in the Declaration of Helsinki. Before trial entry, all patients provide written and informed consent.

In this study, we present 3 co-primary hypotheses: (1) changes in depression scores in the Hamilton Depression Rating Scale 17-item version (HDRS-17) [30], from baseline to endpoint, will be larger in the "double active" compared to the "ptES-only" arm; (2) changes in depression scores (HDRS-17), from baseline to endpoint, will be larger in the "double active" compared to the "double-sham" arm; and (3) changes in depression scores (HDRS-17), from baseline to endpoint, will be larger in the "ptES-only" as compared to the "double-sham" arm. Although fewer co-primary hypotheses could have been theoretically presented, we considered that the 3 of them are sufficiently novel to be appraised, as they (1) test the additive effects of iBT above and beyond ptES, assessing whether the combination is synergistic, (2) evaluate the efficacy of this

remotely-performed combination, and (3) enhance the internal validity of the study, considering unexpected biases that could arise in this “digital” trial that might not necessarily be present in on-site trials (as discussed below).

Our secondary hypotheses are that: (1) changes in depression scores will be larger in "double-active" compared to "ptES-only", in "double-active" compared to "double-sham", and "ptES-only" compared to "double-sham" arms, using additional depression-rating scales (please refer to these scales below, in item 2.4 Procedures); (2) response (defined as ≥ 50%

reduction in HDRS-17) and remission (defined as HDRS-17 ≤ 7) will be larger in "double active" versus "ptES-only", "double-active" versus "double-sham", and "ptES-only" versus "double sham" arms; (3) reduction in comorbid anxiety scores will be greater in "double-active" compared "ptES-only", "double-active" compared to "double-sham", and "ptES-only" compared to "double-sham"; (4) the clinical usability of the "double active" protocol will be regarded as (very) easy by ≥ 80% of recipients, according to a Likert scale; (5) all three protocols will be equally safe and tolerable, according to the tDCS Adverse Events Survey [12].

2.2 Patients

We recruit patients of all genders, from ages 18 to 59, with a clinical diagnosis of MDD per DSM-5 criteria (Diagnostic and Statistical Manual of Mental Disorders, 5th edition) [31]. The study is conducted at the University of São Paulo, Brazil, at two of its institutions: the University Hospital (*Hospital Universitário - HU*) and the Institute of Psychiatry of the Clinics Hospital (*Instituto de Psiquiatria - IPq/HC-FMUSP*).

The inclusion criteria are: (1) a current depressive episode of at least moderate severity, with a baseline score on the HDRS-17 [30] ≥ 17; (2) absence of contraindications to tDCS (i.e., metallic plates on the head, brain devices, brain aneurysm clips, cochlear implants, cardiac pacemakers, among others); (3) 8 or more years of formal education; (4) access to a personal smartphone and internet at home; and (5) lifetime refractoriness to no more than 3 antidepressants, at optimal doses and for an appropriate duration of 6 weeks, according to a modified Antidepressant Treatment History Form (ATHF) [32].

The exclusion criteria are: (1) other psychiatric diagnoses (i.e., schizophrenia, schizoaffective disorder, bipolar disorder, obsessive-compulsive disorder, attention-deficit and hyperactivity disorder, eating disorders, personality disorders, substance use disorders), although anxiety disorders, as comorbidities, are accepted; (2) suicidal ideation or a suicide attempt within 4 weeks or less, prior to baseline; (3) previous or current psychotic symptoms, not otherwise specified; (4) depressive symptoms better explained by other clinical conditions (i.e., hypothyroidism, anemia, congestive heart failure, among others) or other psychiatric disorders; (5) severe clinical conditions, including Post-Acute Sequelae of COVID-19 [33]; (6) epilepsy and/or other neurological disorders; (7) suspected or confirmed pregnancy; (8) lactation; and (9) use of diazepam > 10mg per day (or equivalent doses of other benzodiazepines). Regarding other medications, no antidepressant washout is being performed, and antidepressant medications currently in use should be in stable doses for at least 6 weeks prior to baseline.

Patient recruitment is being performed through advertisements in our group website (www.sin.org.br) and in our social media channels (Facebook: neuropsiquiatria.ipq; Instagram: neuropsiquiatria.ipq; LinkedIn: sin-ipq). We also accept clinical referrals from health professionals. Finally, the press offices of the Institute of

Psychiatry and of the University of São Paulo Medical School also perform periodic announcements regarding our project, with considerable attention from traditional media.

Our screening process consists of two stages. Firstly, interested volunteers answer an online and confidential survey, available through a secure REDCap (Research Electronic Data Capture) link, in order to provide personal contact information and answer basic multiple-choice questions regarding inclusion/exclusion criteria as well as the 9-item Patient Health Questionnaire (PHQ-9) [34]. Subsequently, all survey respondents who have not preliminarily indicated any exclusion criterion, and have achieved a score on the PHQ-9 ≥ 10, are invited for a 45-minute initial online interview, with a research-team psychiatrist, in order to confirm eligibility criteria, according to the Mini-International Neuropsychiatric Interview (MINI) [35]. The two-stage online screening process has proven an asset during the COVID-19 pandemic. Before attending the onsite evaluation, volunteers are screened for COVID-19 symptoms, and if COVID-19 is suspected, a PCR SARS-CoV-2 test is required before the onsite evaluation.

If patients have been considered eligible after these two stages (surveys and online interview), they are invited for an onsite visit in our research centers, for a complete psychiatric evaluation, written and informed consent, baseline assessments, and finally, randomization if enrolled. Moreover, patients will subsequently be invited to receive the two active interventions in: (1) an open-label 6-week crossover phase, if they were previously randomized to "double sham" and do not achieve response at endpoint (defined as ≥ 50% reduction in HDRS-17 scores from baseline to endpoint), and (2) a maximum 6-month open-label follow-up phase if they were previously randomized to "double-active" or "ptES-only" and do achieve response at endpoint. Furthermore, patients who achieve response at the end of the crossover phase are also eligible for the

6-month open-label follow-up phase (**Figure 1**). However, patients who were randomized to "ptES-only", but do not achieve response, will not be eligible for open-label follow-up, as it is unlikely, they would profit from a continuation.

2.3 Interventions

For the combined ptES and iBT, we use tDCS devices and the BT app developed by Flow Neuroscience™ (Malmö, Sweden) (**Figure 2**).

The Flow™ ptES device consists of a one-size-fits-all rechargeable headset, with circular electrodes (area = 22.9cm^2). The anode is placed over the left prefrontal cortex, and the cathode, over the right prefrontal cortex. The device is manufactured with customized, saline pre-humidified and non-reusable sponge pads, which can be easily adjusted over the electrodes, with the aid of circular rubber bands. Flow™ ptES devices are paired, via Bluetooth, to an iBT app (Flow Depression™ - iOS/Android) and provide augmented-reality resources: when patients capture their faces on the smartphone camera, a virtual reality headset is displayed where the actual headset is to be positioned. For PSYLECT, the iBT app has been renamed and the original manufacturer contact information has been replaced with that of our research center.

Flow™ has been approved by health regulatory agencies, for home-use in adult patients with MDD, in the European Union, the United Kingdom, and Brazil (National Agency of Sanitary Health, ANVISA). Moreover, the device has undergone an electric-field (EF) simulation study [36], with 15 brain models obtained from structural MRI from previous clinical trials performed by our team, and displayed compatible EF distributions as compared to those observed in traditional tDCS montages used in those previous studies [37,38]. Furthermore, the Flow device and app have been evaluated in a previous,

open-label pilot phase with 5 depressed patients, at our research center, displaying favorable tolerability, safety, and efficacy profiles [17].

For the active tDCS sessions, current strength is delivered at 2mA (current density = 0.087mA/cm^2), for 30 minutes, daily for 5 continuous days (with a subsequent 2-day pause), during the first 3 weeks, and twice-weekly for the following 3 weeks (comprising a total of 21 sessions in 6 weeks). For the sham tDCS sessions, the protocol is similar, but consists of fade-in and fade-out phases of 1mA, for 45 seconds, at the beginning and at the end of the sessions, with a silent period in between for the remaining 28.5 minutes.

The iBT intervention is performed concomitantly to the tDCS session and consists of an app-based interactive protocol (with a chatbot and online videos), synchronized via Bluetooth, to the tDCS device. For PSYLECT, the chatbot iBT protocol has been translated from English to Portuguese, and all iBT videos are either presented with Portuguese subtitles, or in the case of meditation videos (which allow patients to close their eyes), have been dubbed to Portuguese. Sham iBT consists of free internet browsing.

Arms and Interventions

Arms	Assigned Interventions
Experimental: Double-active Active portable transcranial electrical stimulation (ptES) and active internet-based behavioral therapy (iBT).	Device: Double Active: Active portable transcranial stimulation (ptES) and active internet-based behavioral therapy (iBT) ptES is delivered by the Flow device (Flow Neuroscience, Malmö, Sweden), consisting of a one-size-fits-all, transcranial direct current stimulation (tDCS) headset with circular electrodes (area = 22.9cm2). The anode is positioned over the left prefrontal cortex, and the cathode over the right prefrontal cortex. Current strength is set at 2mA (current density = 0.087mA/cm2) for 30 minutes, daily for 5 continuous days (with a 2-day pause) for the first 3 weeks, with twice-weekly sessions for the following 3 weeks (total of 21 sessions in 6 weeks). Active iBT consists of a smartphone app with an electronic therapist-avatar. The iBT sessions are delivered concomitantly to the tDCS sessions (the tDCS device connects via bluetooth to the participant's smartphone app).
Active Comparator: ptES-only Active portable transcranial electrical stimulation (ptES) and sham internet-based behavioral therapy (iBT).	Device: ptES-only: Active portable transcranial stimulation (ptES) and sham internet-based behavioral therapy (iBT) ptES is delivered by the Flow device (Flow Neuroscience, Malmö, Sweden), consisting of a one-size-fits-all, transcranial direct current stimulation (tDCS) headset with circular electrodes (area = 22.9cm2). The anode is positioned over the left prefrontal cortex, and the cathode over the right prefrontal cortex. Current strength is set at 2mA (current density = 0.087mA/cm2) for 30 minutes, daily for 5 continuous days (with a 2-day pause) for the first 3 weeks, with twice-weekly sessions for the following 3 weeks (total of 21 sessions in 6 weeks). The sham iBT sessions are delivered concomitantly to the active ptES sessions (the ptES device connects via bluetooth to the participant's smartphone app).
Sham Comparator: Double-sham Sham portable transcranial electrical stimulation (ptES) and sham internet-based behavioral therapy (iBT).	Device: Double-sham: Sham portable transcranial stimulation (ptES) and sham internet-based behavioral therapy (iBT) Sham ptES for this trial is delivered by the Flow device (Flow Neuroscience, Malmö, Sweden), consisting of a one-size-fits-all transcranial direct current stimulation (tDCS) headset, with circular electrodes (area = 22.9cm2). The anode is positioned over the left prefrontal cortex, and the cathode over the right prefrontal cortex. The sham protocol consists of a fade-in and fade-out phases of 1mA for 45 seconds, followed by a silent period in between for the remaining 28 1/2 minutes. The sham iBT sessions are delivered concomitantly to the sham ptES sessions (the ptES device connects via bluetooth to the participant's smartphone app).

2.4 Procedures

Upon trial enrollment, patients are initially registered by our research team on the study dashboard, using a personal email as identification. Patients then receive a confirmatory email and are instructed to: (1) download the trial app (in iOS or Android), (2) create their own personal app account and password, which are validated by a trial-provided security code. Randomization (1:1:1) is performed remotely through a computer random generator, using a Mersenne Twister algorithm. Subsequently, patients receive another email for confirmation of trial enrollment, thereby completing the randomization process and trial registration, with preservation of allocation concealment.

Once patients have been enrolled and randomized, their personal accounts become visible for the research team, on the study dashboard, where only the researchers can oversee adherence to, and completion of, home-based trial sessions, all the while remaining blinded. Patients are advised not to describe their app characteristics during the clinical evaluations, for this would unblind the investigators; however, reports of ptES-related adverse events are actively assessed during these online meetings. If unblinding occurs at any point during an evaluation, patients will be referred to another blinded member of the team for the remaining part of the trial. Blinding efficacy assessments for both evaluators and patients are performed at the endpoint.

For the evaluation of depression and anxiety symptoms, we use the following scales: (1) Hamilton Depression Rating Scale, 17-item version (HDRS-17) [30], (2) Montgomery–Åsberg Depression Rating Scale (MADRS) [39], (3) Beck Depression Inventory - II (BDI-II) [40], (4) Positive and Negative Affect Scale (PANAS) [41], and (5) State-Trait Anxiety Inventory (STAI) [42]. To evaluate for treatment-emergent manic or hypomanic symptoms and tDCS-related adverse events, the Young Mania Rating Scale (YMRS) [43] and the tDCS adverse events survey [12] are applied, respectively. We will

report all additional adverse events not otherwise captured by the structured tDCS-related adverse events questionnaire.

Clinical usability of the device is evaluated through a 5-item Likert scale, designed specifically for this trial (which incorporates questions about the ptES device and iBT app). The Edinburgh Handedness Inventory - Short Form [44], the Defined Daily Dose (DDD) medication form [45], and sociodemographic and head measurements (head circumference, nasion-inion and tragus-tragus distances) are collected at baseline. The Clinical Global Impression Rating (CGI) form is applied at baseline and endpoint [46] (**Table 1**).

	Baseline	W1	W2	W3	W4	W5	W6
Sociodemographic data/ head measurements	✓						
Edinburgh Handedness Inventory (short version)	✓						
DDD	✓						
HDRS-17	✓		✓	✓	✓		✓
HAM-A	✓			✓			✓
MADRS	✓		✓	✓	✓		✓
CGI	✓			✓			✓
YMRS	✓		✓	✓	✓		✓
Blinding assessment - evaluator							✓
Blinding assessment - patient							✓

PANAS	✓			✓			✓
STAI-T	✓			✓			✓
STAI-S	✓			✓			✓
BDI - II	✓			✓			✓
LIkert usability scale		✓	✓	✓	✓	✓	✓
tDCS side effect questionnaire		✓	✓	✓	✓	✓	✓

Table 1. Clinical scales and questionnaires used during Psylect. Abbreviations: DDD: Defined Daily Dose; HDRS-17: Hamilton Depression Rating Scale, 17-item version; HAM-A: Hamilton Anxiety Rating Scale; MADRS: Montgomery-Åsberg Depression Rating Scale; CGI: Clinical Global Impression; YMRS: Young Mania Rating Scale; PANAS: Positive and Negative Affect Rating Scale; STAI-T/STAI: State-Trait Anxiety Inventory; BDI-II: Beck Depression Inventory - II; tDCS: transcranial direct current stimulation.

The first ptES session of each patient is performed at our research centers, with direct supervision of unblinded members of our team, who are not directly involved with clinical evaluations. These members need to be unblinded once they offer consultations regarding app usage. In this initial training session, the different parts of the equipment are presented to the patients, as well as recommendations on when to interrupt the session (i.e., presence of pain or any serious discomfort). If any difficulties are detected during the initial training session, additional onsite training sessions can be scheduled. Once patients are deemed trained for ptES, all further sessions are performed without supervision at the patients' homes, with recommendations to remain at physical rest (sitting or lying down), throughout the session, in a calm environment and concentrated on the app´s instructions. The app offers a tutorial on how to correctly place the headset, before each individual session, and informs patients to remove the headset after session completion. The app also notifies patients when the headset needs recharging, and sets

off reminders for subsequent sessions, which can be performed after a minimum interval of 24 hours. Missed sessions can be rescheduled for the upcoming weeks, with no more than 5 sessions per week.

Patients are evaluated online on a weekly basis by the blinded members of the research staff. Moreover, all trial patients have remote access to supervision upon request by unblinded members of the team. For this purpose, we provide a mobile number for immediate contact. If medical attention is deemed necessary, due to an intercurrence or significant adverse event, an online medical appointment is performed within 48 hours. If needed, patients can also be referred to an onsite clinical evaluation at our research centers. Furthermore, adherence and completion of sessions are monitored online, through the study dashboard. Early unblinding and trial discontinuation before study completion are initiated by the following circumstances: (1) significant depression worsening, defined as a > 25% increase in HDRS-17 scores from baseline, during two consecutive weekly assessments; (2) development of suicidal ideation or suicide attempt; (3) development of psychotic symptoms; (4) development of (hypo)mania and/or clinically significant mixed symptoms (YMRS ≥ 8); (5) low adherence to study protocol, defined as < 75% of completed sessions, at any point during the study; (6) absence at any weekly evaluation without justification; and (7) patient consent withdrawal.

After trial completion, the endpoint assessments will be completed by blinded members of our research team. As a final step, patients and clinical evaluators will be unblinded using the study dashboard, and eligibility for the crossover and follow-up stages will be assessed. If participation in the study is terminated at the endpoint assessment, patients are referred to their original treatment facilities.

2.5 Digitalization

The Psylect trial has been conceived as a trial with a partial degree of digitization - i.e., although the trial involves onsite evaluations and patient training, it also makes use of online technologies to "improve recruitment and retention, data collection, and analytics" [47]. We perform digital procedures to screen and recruit patients, perform weekly clinical assessments of enrolled patients (from weeks 1 to 5; baseline and endpoint assessments are performed onsite), remotely monitor adherence to the home-based study protocol, receive responses of self-administered surveys and questionnaires (through the REDCap platform). Furthermore, instructional online videos for correct positioning of the headset and Bluetooth connection to the smartphones, for the active and sham BT interventions, are also offered online.

2.6 Data Management

Study data are collected and managed using REDCap (Research Electronic Data Capture). REDCap is a secure, web-based software platform designed to support data capture for research studies, providing: 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources [48,49]. REDCap can be installed in a variety of environments, in compliance with international standards, such as HIPAA (Health Insurance Portability and Accountability Act), CFR (Code of Federal Regulations) Title 21/Part 11, FISMA (Federal Information

Security Management Act), and Brazilian data management regulations (*Lei Geral de Proteção de Dados - LGPD*).

Data will be coded according to a previously developed data dictionary. Quality of data collection will be monitored by random data quality checks for consistency (e.g., depression scores compatible in different scales) and completeness (absence or few cases of missing data).

2.7 Sample Size Calculation

For Psylect, we estimated a total sample size (n) of 210 randomized patients (70 patients per arm), to achieve the ability to observe statistically significant effects, with a power of 80% ($1-\beta = 0.8$). Dropouts were assumed to increase monotonically (Weibull) and to be equally distributed between arms. We will use 4 measurements (continuous linear change from baseline, weeks 2, 4 and endpoint), between the 3 arms (time x group interaction), in the framework of linear mixed-effects models (LMM) [50,51].

For our sample size calculations, we assumed baseline depression scores and standard deviation (SD) of 25 (±5) on the HDRS-17, distributed equally between groups, based on previous works from our group [37,38,52]. Furthermore, we considered that: (1) placebo effects in the double-sham arm will impact baseline depression scores equal to 1 effect size (ES) in SD units (ES = difference in mean change divided by SD); (2) the "ptES-only" arm will have the same placebo effects present in the double-sham arm (ES = 1), plus a treatment response of ES = 0.4; and, (3) the "double-active" arm will have placebo effects (ES = 1) plus a larger response of ES = 0.8. Therefore, probable endpoint scores of 20, 18 and 16 were used, for "double-sham", "ptES-only" and "double-active", respectively. The effect sizes were also chosen based on the results from our previous

trials and considering that tDCS and online behavioral therapies have small to moderate effect sizes.

Sample size per arm was calculated based on the smallest detectable group difference (ES tDCS vs. combination = -0.4, ES placebo vs. tDCS = -0.4). Significance levels were Bonferroni corrected for 3-way pairwise comparisons ($\alpha = 0.05/3$) to control family-wise error rate, while still allowing for more anti-conservative adjustment in the final analysis [53–55].

2.8 Statistical analysis

As we have 3 co-primary hypotheses, each co-primary hypothesis will be considered statistically significant if a two-sided $p<0.0167$ (Bonferroni-corrected) is obtained. For the analysis of the coprimary outcomes, LLM will be employed, using a first order regressive covariance structure, which includes all observed variables without the need of imputing missing data. The dependent variable is score change on the HDRS-17. Independent variables are time (all observations until week 6), and group ("double-active", "ptES-only" and "double-sham"). We will test the statistical significance between the pairwise comparisons per our primary hypotheses. We will employ an intention-to-treat (ITT) approach.

For the analysis of the secondary outcomes, linear mixed-effects models will be employed analogically to the analysis for the primary outcomes. Binary outcomes (response and remission) will be modeled using mixed logistic regression at each timepoint. Improvement in other depressive domains will be evaluated using the same linear hierarchical models described.

3. Discussion

Psylect will compare the efficacy, safety, tolerability and usability of: (1) a combined and active regimen of ptES and iBT compared to active ptES in monotherapy; (2) a combined and active regimen of ptES and iBT compared to a double sham counterpart; and (3) active ptES in monotherapy versus a double sham, for the treatment of MDD, in adult patients, during 6 weeks. Antidepressant medications currently in use at baseline will be maintained throughout the trial, in stable doses.

After two RCTs developed by our team that have, respectively, studied the combination of tDCS and an antidepressant in a factorial design [38], and the non-inferiority of tDCS in comparison to an antidepressant [37], in PSYLECT we aim to evaluate the combination of a home-based tDCS protocol with an internet-based behavioral therapy approach.

Neurobehavioral strategies have been increasingly associated with tDCS for the treatment of MDD and other mental disorders, initially inspired by positive results with the combination of tES and motor rehabilitation for the treatment of stroke [19,20]. The neurobiological rationale behind these combinations is based on the "state dependency" of targeted neural circuits [19], with recent evidence suggesting that ongoing neural activity is necessary for tDCS to bring forth neuroplastic effects, especially with concurrent interventions [20]. Previously, Segrave et al. studied the combination of tDCS with cognitive-control training (CCT) in 27 patients with MDD, and observed that the combined treatment demonstrated superior efficacy when compared to either treatment alone, in the reduction of MADRS scores, after 3 weeks [21]. Brunoni et al. (2014) [22] also studied the treatment effect of concurrent tDCS and CCT in 37 patients with MDD. In this study, although both arms (active CCT + active tDCS and active CCT + sham tDCS)

displayed similar improvements, it was observed that among patients who received active tDCS, a greater reduction in depressive symptoms was observed in older individuals with better performance in speed and flexibility of information processing, possibly indicating greater engagement of the DLPFC [22]. Recently, another pilot study (n = 31) observed that the combination of tDCS and mindfulness-based cognitive therapy in depressed patients was superior in the maintenance of clinical improvement at a follow-up assessment, as compared to tDCS alone, strengthening the hypothesis that a combined approach could offer therapeutic advantages over tDCS in monotherapy [56].

Despite these advancements in tDCS research and methodology, patient access to the technique is still limited, mainly for logistical reasons. Daily tDCS sessions, performed over several weeks, in clinical or research facilities, can present a challenge to patients, especially in pandemic scenarios [57]. On the other hand, home-use tDCS devices have only recently been developed. Guidelines for conducting research with tDCS at home already exist [18], but few trials have investigated this procedure. An open-label pilot study (n=34) [16] and a case series (n=5) [17] have observed that home-use tDCS for MDD could be feasible, safe and tolerable.

In line with the rationale in the paragraph above, we understand that psychological interventions (i.e., neurocognitive interventions, such as psychoeducation or behavioral activation) performed in research facilities could also present similar logistical challenges. In this sense, it is noteworthy that these remote interventions have been used for depression in the last 30 years, according to the available technology in each period (for example, through books, phone calls, software, text messages and, more recently, through smartphone apps). Automated programs are usually carried out through interactive modules and multimedia techniques (photos, advice, sketches and videos), to engage and motivate patients, generally in an add-on strategy to first-line

treatments. Online interventions can be multifaceted, including cognitive training, self-monitoring of mood, mindfulness, psychoeducation, behavioral activation, and cognitive bias modification [58]. A positive trend was observed for fully automated applications and for interventions that provided user feedback (i.e., statistics and progress) [58].

However, one limitation of online psychological interventions [58] is the lack of a clinically verified MDD diagnosis in enrolled patients. This shortcoming was addressed by Josephine et al. (2017), who conducted a systematic review of CBT apps in the treatment of clinically diagnosed MDD [25]. Reviewing data from 19 selected studies, the authors still observed a statistically significant pooled effect size [Hedge's g=−0.90, (95% CI: −1.07,−0.73; I2 = 0%)], favoring the active interventions over waiting lists [25]. However, only a small minority of online interventions are supported by controlled studies and many might profit from the "digital placebo effect", characterized as "placebo-like effects seen from mobile health interventions, such as smartphone apps, and which can influence the overall therapeutic response [59]. In PSYLECT, we use a sham app, instead of no intervention, in consonance with our endeavor to better quantify the digital placebo effect. Furthermore, hundreds of apps are currently available for the treatment of depression, but few studies have been carried out comparing the effect of these internet-based interventions versus sham, in real-life scenarios, and with larger and more heterogeneous clinical samples [60]. Moreover, only a small minority of commercially available mental health apps are supported by evidence from controlled studies [29].

3.1 Limitations and challenges

The use of digital features within a trial using remote interventions, such as ours, present both new opportunities and challenges. Regarding opportunities, this approach

can overcome some of the main difficulties of on-site tDCS trials, such as the need of daily visits for several weeks due to treatment schedule and allocating staff for device manipulation. By performing the trial remotely, dislocation burdens are non-existent, as well as the physical need for space at the hospital, and trained staff for delivering tDCS sessions, aspects that increase trial length (usually, the person delivering tDCS sessions can monitor only 2-3 people at once, and physical constraints make delivering several sessions per day difficult). In contrast, a single member of the team can monitor several people using ptES devices at home simultaneously. This aspect is further leveraged by using methods for recruiting potential patients in large catchment areas via social media and Internet.

About challenges, there are many unique, specific methodological aspects that operate differently. For instance, randomization and allocation are markedly different in digital trials compared to the traditional SNOSE method (sequentially numbered, opaque, and sealed envelopes) used in many onsite trials. There are also risks of cyber-hacking and data security breaches, making digital clinical trials more vulnerable to these hazards. Moreover, there are concerns that patients can discuss their participation in PSYLECT in online forums (e.g., reddit) or social media, including taking pictures of the app and the device, even if they are instructed not to do so.

Finally, it is unclear whether external validity is increased or decreased in our study. While it could be argued that a greater sample diversity will be achieved due to ease of access to potential patients, it is also possible that a specific population of people are being contacted and enrolled preferentially, representing those more educated, more digitally literate, and more prone to embrace new technologies. It is also unclear whether we should expect higher or lower levels of attrition compared to onsite trials. On the one hand, not needing to return daily to the clinical center could decrease burden and

minimize dropouts. On the other hand, patients from digital trials might show less engagement and more difficulties in self-delivering the sessions. The lack of daily contact with the clinical staff might eventually decrease motivation and increase dropouts. All these aspects will be carefully monitored in our ongoing study.

4. Conclusions

tDCS has proven a safe, tolerable, and effective strategy for the treatment of MDD. The moderate effect size of the intervention and the logistical issues associated with daily visits to research and/or clinical facilities has created interest in the evaluation of new approaches, such as home-based, remotely supervised regimens and the combination of tDCS with psychological interventions. These new strategies are still in their nascent stages, with preliminary and positive data derived from small, pilot trials. In this regard, PSYLECT will be an RCT with a large sample size, to evaluate the effectiveness, safety, tolerability, and feasibility of ptES associated with iBT, as compared to ptES in monotherapy and double sham, for the treatment of MDD, in adult patients.

Funding details

The trial is sponsored by the public governmental agency FAPESP (São Paulo Research State Foundation) Thematic Grant (2019/06009-6). Flow Neuroscience™ donated a small budget that was used solely for paying clinical and research staff directly involved in the trial. Flow Neuroscience™ and FAPESP have no role in the study design, statistical analysis, and manuscript writing of any publication from PSYLECT.

References

[1] Collaborators GBD. … national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis …. 2018; Available from: https://leicester.figshare.com/articles/journal_contribution/Global_regional_and_national_incidence_prevalence_and_years_lived_with_disability_for_354_diseases_and_injuries_for_195_countries_and_territories_1990-2017_a_systematic_analysis_for_the_Global_Burden_of_Disease_Study_2017_/10200149/files/18383459.pdf.

[2] Nemeroff CB. Prevalence and management of treatment-resistant depression. J Clin Psychiatry. 2007;68 Suppl 8:17–25.

[3] Rush AJ, Trivedi MH, Wisniewski SR, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Am J Psychiatry. 2006;163:1905–1917.

[4] Anderson IM, Ferrier IN, Baldwin RC, et al. Evidence-based guidelines for treating depressive disorders with antidepressants: a revision of the 2000 British Association for Psychopharmacology guidelines. J Psychopharmacol. 2008;22:343–396.

[5] Keller MB, McCullough JP, Klein DN, et al. A comparison of nefazodone, the cognitive behavioral-analysis system of psychotherapy, and their combination for the treatment of chronic depression. N Engl J Med. 2000;342:1462–1470.

[6] Razza LB, Palumbo P, Moffa AH, et al. A systematic review and meta-analysis on the effects of transcranial direct current stimulation in depressive episodes. Depress Anxiety [Internet]. 2020; Available from: http://dx.doi.org/10.1002/da.23004.

[7] Milev RV, Giacobbe P, Kennedy SH, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder: Section 4. Neurostimulation Treatments. Can J Psychiatry. 2016;61:561–575.

[8] Lefaucheur J-P, Antal A, Ayache SS, et al. Evidence-based guidelines on the therapeutic use of transcranial direct current stimulation (tDCS). Clin Neurophysiol. 2017;128:56–92.

[9] Fregni F, El-Hagrassy MM, Pacheco-Barrios K, et al. Evidence-based guidelines and secondary meta-analysis for the use of transcranial direct current stimulation (tDCS) in neurological and psychiatric disorders. Int J Neuropsychopharmacol [Internet]. 2020; Available from: http://dx.doi.org/10.1093/ijnp/pyaa051.

[10] Borrione L, Moffa AH, Martin D, et al. Transcranial Direct Current Stimulation in the Acute Depressive Episode: A Systematic Review of Current Knowledge. J ECT. 2018;34:153–163.

[11] Brunoni AR, Sampaio-Junior B, Moffa AH, et al. Noninvasive brain stimulation in psychiatric disorders: a primer. Braz J Psychiatry. 2019;41:70–81.

[12] Aparicio LVM, Guarienti F, Razza LB, et al. A Systematic Review on the Acceptability and Tolerability of Transcranial Direct Current Stimulation Treatment in Neuropsychiatry Trials. Brain Stimul. 2016;9:671–681.

[13] Grimm S, Beck J, Schuepbach D, et al. Imbalance between Left and Right Dorsolateral Prefrontal Cortex in Major Depression Is Linked to Negative Emotional Judgment: An fMRI Study in Severe Major Depressive Disorder. Biol Psychiatry. 2008;63:369–376.

[14] Kaiser RH, Andrews-Hanna JR, Wager TD, et al. Large-Scale Network Dysfunction in Major Depressive Disorder: A Meta-analysis of Resting-State Functional Connectivity. JAMA Psychiatry. 2015;72:603–611.

[15] Williams LM. Precision psychiatry: a neural circuit taxonomy for depression and anxiety. Lancet Psychiatry. 2016;3:472–480.

[16] Alonzo A, Fong J, Ball N, et al. Pilot trial of home-administered transcranial direct current stimulation for the treatment of depression. J Affect Disord. 2019;252:475–483.

[17] Borrione L, Klein I, Razza LB, et al. Use of app-based psychological interventions in combination with home-use transcranial direct current stimulation for the treatment of major depressive disorder: A case series. J Affect Disord. 2021;288:189–190.

[18] Charvet LE, Shaw MT, Bikson M, et al. Supervised transcranial direct current stimulation (tDCS) at home: A guide for clinical research and practice. Brain Stimul. 2020;13:686–693.

[19] Sathappan AV, Luber BM, Lisanby SH. The Dynamic Duo: Combining noninvasive brain stimulation with cognitive interventions. Prog Neuropsychopharmacol Biol Psychiatry. 2019;89:347–360.

[20] Dedoncker J, Baeken C, De Raedt R, et al. Combined transcranial direct current stimulation and psychological interventions: State of the art and promising perspectives for clinical psychology. Biol Psychol. 2021;158:107991.

[21] Segrave RA, Arnold S, Hoy K, et al. Concurrent cognitive control training augments the antidepressant efficacy of tDCS: a pilot study. Brain Stimul. 2014;7:325–331.

[22] Brunoni AR, Boggio PS, De Raedt R, et al. Cognitive control therapy and transcranial direct current stimulation for depression: a randomized, double-blinded, controlled trial. J Affect Disord. 2014;162:43–49.

[23] Li J, Theng Y-L, Foo S. Game-based digital interventions for depression therapy: a systematic review and meta-analysis. Cyberpsychol Behav Soc Netw. 2014;17:519–527.

[24] Ben-Zeev D, Brian RM, Jonathan G, et al. Mobile Health (mHealth) Versus Clinic-Based Group Intervention for People With Serious Mental Illness: A Randomized Controlled Trial. Psychiatr Serv. 2018;69:978–985.

[25] Josephine K, Josefine L, Philipp D, et al. Internet- and mobile-based depression interventions for people with diagnosed depression: A systematic review and meta-analysis. J Affect Disord. 2017;223:28–40.

[26] Linardon J, Cuijpers P, Carlbring P, et al. The efficacy of app-supported smartphone interventions for mental health problems: a meta-analysis of randomized controlled trials. World Psychiatry. 2019;18:325–336.

[27] Torous J, Lipschitz J, Ng M, et al. Dropout rates in clinical trials of smartphone apps for depressive symptoms: A systematic review and meta-analysis. J Affect Disord.

2020;263:413–419.

[28] Psychiatry TL, The Lancet Psychiatry. Digital psychiatry: moving past potential [Internet]. The Lancet Psychiatry. 2021. p. 259. Available from: http://dx.doi.org/10.1016/s2215-0366(21)00096-1.

[29] Torous J, Bucci S, Bell IH, et al. The growing field of digital psychiatry: current evidence and the future of apps, social media, chatbots, and virtual reality. World Psychiatry. 2021;20:318–335.

[30] Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry. 1960;23:56–62.

[31] American Psychiatric Association AP, Association AP, Others. Diagnostic and statistical manual of mental disorders: DSM-5 [Internet]. Washington, DC: American psychiatric association; 2013. Available from: https://bukg.pw/diagnostic-and-statistical-manual-of-mental-disorders-dsm-5.pdf.

[32] Dew RE, Kramer SI, McCall WV. Adequacy of antidepressant treatment by psychiatric residents: the antidepressant treatment history form as a possible assessment tool. Acad Psychiatry. 2005;29:283–288.

[33] Carfì A, Bernabei R, Landi F, et al. Persistent Symptoms in Patients After Acute COVID-19. JAMA. 2020;324:603–605.

[34] Kroenke K, Spitzer RL, Williams JBW. The PHQ-9 [Internet]. Journal of General Internal Medicine. 2001. p. 606–613. Available from: http://dx.doi.org/10.1046/j.1525-1497.2001.016009606.x.

[35] Sheehan DV, Lecrubier Y, Sheehan KH, et al. The validity of Mini International Neuropsychiatric Interview (MINI). The development and validation of a structured diagnostic interview for DSM-IV and ICD-10. J Clin Psychiatry. 1998;59:211–232.

[36] Borrione L, Suen PJC, Razza LB, et al. The Flow brain stimulation headset for the treatment of depression: overview of its safety, efficacy and portable design. Expert Rev Med Devices. 2020;17:867–878.

[37] Brunoni AR, Moffa AH, Sampaio-Junior B, et al. Trial of Electrical Direct-Current Therapy versus Escitalopram for Depression. N Engl J Med. 2017;376:2523–2533.

[38] Brunoni AR, Valiengo L, Baccaro A, et al. The sertraline vs. electrical current therapy for treating depression clinical study: results from a factorial, randomized, controlled trial. JAMA Psychiatry. 2013;70:383–391.

[39] Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry. 1979;134:382–389.

[40] Beck AT, Steer RA, Brown GK. BDI-II, Beck Depression Inventory: Manual. Psychological Corporation; 1996.

[41] Pires P, Filgueiras A, Ribas R, et al. Positive and negative affect schedule: psychometric properties for the Brazilian Portuguese version. Span J Psychol. 2013;16:E58.

[42] Andrade L, Gorenstein C, Vieira Filho AH. Psychometric properties of the Portuguese version of the State-Trait Anxiety Inventory applied to college students: factor analysis and relation to the Beck …. Brazilian Journal of [Internet]. 2001; Available from: https://www.scielo.br/scielo.php?pid=S0100-

879X2001000300011&script=sci_arttext.

[43] Young RC, Biggs JT, Ziegler VE, et al. A rating scale for mania: reliability, validity and sensitivity. Br J Psychiatry. 1978;133:429–435.

[44] Veale JF. Edinburgh Handedness Inventory - Short Form: a revised version based on confirmatory factor analysis. Laterality. 2014;19:164–177.

[45] Wertheimer AI. The defined daily dose system (DDD) for drug utilization review. Hosp Pharm. 1986;21:233–234, 239–241, 258.

[46] Kadouri A, Corruble E, Falissard B. The improved Clinical Global Impression Scale (iCGI): development and validation in depression. BMC Psychiatry. 2007;7:7.

[47] Inan OT, Tenaerts P, Prindiville SA, et al. Digitizing clinical trials. NPJ Digit Med. 2020;3:101.

[48] Harris PA, Taylor R, Thielke R, et al. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009;42:377–381.

[49] Harris PA, Taylor R, Minor BL, et al. LO‟ Neal, L McLeod, G Delacqua, F Delacqua, J Kirby, SN Duda, REDCap Consortium, The REDCap consortium: Building an international community of software partners. J Biomed Inform. 2019;

[50] Raudenbush SW, Xiao-Feng L. Effects of study duration, frequency of observation, and sample size on power in studies of group differences in polynomial change. Psychol Methods. 2001;6:387–401.

[51] Galbraith S, Marschner IC. Guidelines for the design of clinical trials with

longitudinal outcomes. Control Clin Trials. 2002;23:257–273.

[52] Brunoni AR, Valim C, Fregni F. Combination of noninvasive brain stimulation with pharmacotherapy. Expert Rev Med Devices. 2011;8:31–39.

[53] Sankoh AJ, D'Agostino RB Sr, Huque MF. Efficacy endpoint selection and multiplicity adjustment methods in clinical trials with inherent multiple endpoint issues. Stat Med. 2003;22:3133–3150.

[54] Howard DR, Brown JM, Todd S, et al. Recommendations on multiple testing adjustment in multi-arm trials with a shared control group [Internet]. Statistical Methods in Medical Research. 2018. p. 1513–1530. Available from: http://dx.doi.org/10.1177/0962280216664759.

[55] Proschan MA, Waclawiw MA. Practical guidelines for multiplicity adjustment in clinical trials. Control Clin Trials. 2000;21:527–539.

[56] Monnart A, Vanderhasselt M-A, Schroder E, et al. TREATMENT OF RESISTANT DEPRESSION: A PILOT STUDY ASSESSING THE EFFICACY OF A tDCS-MINDFULNESS PROGRAM COMPARED TO A tDCS-RELAXATION PROGRAM. Front Psychiatry. 2019;10:730.

[57] Bikson M, Hanlon CA, Woods AJ, et al. Guidelines for TMS/tES clinical services and research through the COVID-19 pandemic. Brain Stimul. 2020;13:1124–1149.

[58] Firth J, Torous J, Nicholas J, et al. The efficacy of smartphone-based mental health interventions for depressive symptoms: a meta-analysis of randomized controlled trials. World Psychiatry. 2017;16:287–298.

[59] Torous J, Firth J. The digital placebo effect: mobile mental health meets clinical psychiatry. Lancet Psychiatry. 2016;3:100–102.

[60] Anthes E. Mental health: There's an app for that [Internet]. Nature. 2016. p. 20–23. Available from: http://dx.doi.org/10.1038/532020a.

Summary of changes

	Original Protocol	Final Protocol	Summary of changes
Design	3-arm, parallel, randomized, sham-controlled clinical trial	3-arm, parallel, randomized, sham-controlled clinical trial	No change.
Primary aim	The aim is to study the effect of mobile transcranial direct current stimulation (tDCS) combined with a psychological digital intervention (DI), **compared to double placebo**, in adult patients with unipolar depression, without concomitant use of antidepressant medications, during a period of 6 weeks.	The aim is to study the effect of mobile transcranial direct current stimulation (tDCS) combined with a psychological digital intervention (DI), **compared to mobile tDCS-only and double placebo**, in adult patients with unipolar depression, without concomitant use of antidepressant medications, during a period of 6 weeks.	We included the comparison of the **mobile tDCS-only arm** in the primary aim in order to: (1) evaluate the additive effects of the DI above and beyond tDCS; and (2) preserve the internal validity of the study, considering that unexpected biases could arise in this digital trial that might not necessarily be present in on-site trials. **Note**: The mobile tDCS-only arm was present in the original protocol, but for secondary aims/analyses.
Primary hypothesis	**Our main hypothesis is that the combined treatment is superior to the double placebo** in reducing depressive symptoms throughout a 6-week treatment protocol.	We hypothesized that, after six weeks of treatment, **both active treatment groups (combined and mobile tDCS-only) would be clinically superior to the sham group, with the combined treatment group presenting a greater antidepressant effect.**	We included the comparison of the the **mobile tDCS-only arm** in the primary hypothesis in order to: (1) evaluate the additive effects of the DI above and beyond tDCS, (2) preserve the internal validity of the study, considering unexpected biases that could arise in this digital trial that might not necessarily be present in on-site

			trials. **Note**: The mobile tDCS-only arm was present in the original protocol, but for secondary aims/analyses.
Secondary aims	The secondary aims of Psylect include examining: (1) secondary depression scales; (2) clinical response and remission scales; (3) tolerability/acceptability; (4) **clinical predictors of response;** (5) **cognitive outcomes**; and (6) clinical usability of mobile transcranial direct current stimulation (tDCS).	The secondary objectives of Psylect include examining: (1) secondary depression and **anxiety scales**; (2) clinical response and remission scales; (3) tolerability/acceptability; (4) clinical usability of mobile transcranial direct current stimulation (tDCS).	Inclusion of anxiety scales to better understand the effects of the intervention in comorbid anxiety. Removal of predictors of response and cognitive outcomes.
Secondary hypotheses	We expect the combined intervention to be superior to mobile tDCS in monotherapy and double-sham in secondary scales of depression, clinical response and remission rates. For item (3),we anticipate that all groups will have similar rates of adverse events. For item (6), we expect that >80% of the participants will evaluate the use of mobile transcranial direct current stimulation (tDCS) as (very) easy.	We expect the combined intervention to be superior to mobile tDCS in monotherapy and double-sham in secondary scales of depression **and anxiety scales**, clinical response and remission rates. For item (3),we anticipate that all groups will have similar rates of adverse events. For item (4), we expect that >80% of the participants will evaluate the use of mobile transcranial direct current stimulation (tDCS) as (very) easy.	Inclusion of anxiety scales to better understand the effects of the intervention in comorbid anxiety. Removal of predictors of response and cognitive outcomes.
Randomization	Randomization (1:1:1) is performed remotely through a computer random generator.	Randomization (1:1:1) is performed remotely through a computer random generator, **using a Mersenne Twister algorithm. The randomization list was protected by cryptography and was only broken after the analyses of all a priori hypotheses.**	Implementation of a Mersenne Twister algorithm for remote randomization in the final protocol.
Allocation	Allocation was concealed via an app (Flow Neuroscience [2021], Projeto Psylect [app version 2.14.0]) that seamlessly assigned the participants' group	Allocation was concealed via an app (Flow Neuroscience [2021], Projeto Psylect [app version 2.14.0]) that seamlessly assigned the participants' group	No change.

	after their online registration.	after their online registration.	
Blinding	Double-blind	Double-blind	No change.
Inclusion criteria	The inclusion criteria are: (a) age between 18 and 59 years; (b) initial score on the Hamilton Rating Scale, 17 items (HAMD17) ≥ 17 at the time of screening and initial evaluation; (c) at least 8 years of schooling; (d) availability to use smartphone applications (i.e., having a smartphone with internet access).	The inclusion criteria are: (a) age between 18 and 59 years; (b) initial score on the Hamilton Rating Scale, 17 items (HAMD17) ≥ 17 at the time of screening and initial evaluation; (c) at least 8 years of schooling; (d) availability to use smartphone applications (i.e., having a smartphone with internet access).	No change.
Exclusion criteria	The exclusion criteria are: (a) previous episodes of mania/hypomania or diagnosis of bipolar affective disorder; (b) contraindications for the use of tDCS, such as metal plates in the head; (c) suicidal ideation with planning, or suicide attempt in the last 4 weeks; (d) refractoriness to more than 3 treatments with antidepressant drugs; (e) pregnancy; (f) other psychiatric diagnoses, such as schizophrenia, substance dependence, personality disorders, among others (anxiety disorders as a comorbidity will be included); (g) severe clinical and neurological conditions; (h) depressive symptoms better explained by other clinical conditions (hypothyroidism, anemia, etc.) or by other psychiatric disorders.	The exclusion criteria are: (a) previous episodes of mania/hypomania or diagnosis of bipolar affective disorder; (b) contraindications for the use of tDCS, such as metal plates in the head; (c) suicidal ideation with planning, or suicide attempt in the last 4 weeks; (d) refractoriness to more than 3 treatments with antidepressant drugs; (e) pregnancy; (f) other psychiatric diagnoses, such as schizophrenia, substance dependence, personality disorders, among others (anxiety disorders as a comorbidity will be included); (g) severe clinical and neurological conditions; (h) depressive symptoms better explained by other clinical conditions (hypothyroidism, anemia, etc.) or by other psychiatric disorders.	No change.
tDCS intervention	For the application of tDCS sessions, we will use portable devices called Flow™ (Flow Neuroscience, Malmö, Sweden). The anode and cathode will be positioned over the left and right dorsolateral prefrontal cortex (DLPFC), respectively. We will use a current of 2mA over a circular surface area of 22.9 cm^2 (current density =	For the application of tDCS sessions, we will use portable devices called Flow™ (Flow Neuroscience, Malmö, Sweden). The anode and cathode will be positioned over the left and right dorsolateral prefrontal cortex (DLPFC), respectively. We will use a current of 2mA over a circular surface area of 22.9 cm2 (current density =	Final protocol provided 21 total sessions, instead of 24 sessions. Further details of sham tDCS included in the final protocol.

	0.09mA/cm^2), for a duration of 30 minutes, using pre-moistened and salted custom-made sponges. **Fifteen tDCS sessions will be conducted six times per week during the first three weeks, and two sessions per week until week 6 (totaling 24 sessions).**	0.09mA/cm2), for a duration of 30 minutes, using pre-moistened and salted custom-made sponges. **Fifteen tDCS sessions will be conducted five times per week during the first three weeks, and two sessions per week until week 6 (totaling 21 sessions).** **For the sham tDCS sessions, the protocol is similar, but consists of fade-in and fade-out phases of 1 mA, for 45 seconds, at the beginning and at the end of the sessions, with a silent period in between for the remaining 28.5 minutes.**	
DI intervention	The tDCS intervention will be conducted through the Flow - Depression mobile application (available on iOS or Android) developed by Flow™, which utilizes various modules of behavioral therapy. For each session, a different module is offered, encompassing six main types: nutrition (3 sessions), meditation (4 sessions), physical exercise (3 sessions), sleep hygiene (4 sessions), relapse prevention (4 sessions), and behavioral activation (4 sessions). Additionally, there will be introductory and final sessions. The sham intervention consisted of free internet browsing, delivered through the same interface.	The tDCS intervention will be conducted through the Flow - Depression mobile application (available on iOS or Android) developed by Flow™, which utilizes various modules of behavioral therapy The intervention had 7 modules, each of which containing short (~ 5 min) sessions: introduction (n=5 sessions), behavioral activation (n=5), mindfulness (n=8), physical exercises (n=8), healthy diet (n=10), sleep hygiene (n=7), and planning the future (n=3). Moreover, they could spend additional time in the app when completing daily diaries. All content was offered in Brazilian Portuguese and curated by our team 11. The sham intervention consisted of free internet browsing, delivered through the same interface.	The DI intervention in final protocol consisted of more detailed sessions in each module, comprising a greater number of sessions (during implementation of the original protocol, the app had not undergone complete translation to Brazilian Portuguese).
Adverse events	tDCS-related adverse events (AEs) were evaluated per a commonly used tDCS AE questionnaire.	tDCS-related adverse events (AEs) were evaluated per a commonly used tDCS AE questionnaire.	No changes.
General	For continuous outcomes, we	For continuous outcomes, we	No change.

statistical analysis	used 2-level linear mixed-effects regression models (LMM), assuming a linear relationship over time. LMMs included a discrete factor for the treatment group, a continuous time factor over 5-time points (baseline and weeks 2, 3, 4, and 6), and their interaction as fixed effects, and patient as a random effect.	used 2-level linear mixed-effects regression models (LMM), assuming a linear relationship over time. LMMs included a discrete factor for the treatment group, a continuous time factor over 5-time points (baseline and weeks 2, 3, 4, and 6), and their interaction as fixed effects, and patient as a random effect.	
Outcomes	The primary outcome was the endpoint change in the Hamilton Depression Rating Scale, 17-item version (HDRS-17).	The primary outcome was the endpoint change in the Hamilton Depression Rating Scale, 17-item version (HDRS-17).	No change.

Original Statistical Analysis Plan

Sample size calculation: Based on previous work, we assumed baseline depression scores and standard deviation (SD) of 25 (± 5) on the Hamilton depression rating scale distributed equally between groups. Placebo effect would impact baseline depression scores in one effect size (ES) in SD units (ES = difference in mean change divided by SD). TDCS monotherapy would have a response of ES = 0.4 when compared to placebo and the combination of tDCS and iBT would have a larger response of ES = 0.8 when compared to placebo. Therefore, endpoint scores of 20, 18 and 16 were used. Total sample size (N) was determined to adequately power ($1-\beta = 0.8$) statistical tests for differences in change over 4 measurements (continuous linear change) between treatment arms (time x group interaction) in the framework of linear hierarchical models (LMM). 167,168 Following CONSORT-guideline extensions for the planning of multi-arm parallel-group randomized trials 169, power was not calculated for a global test of significance (e.g. global F-test) but for all combinations of planned pairwise comparisons (placebo vs. tDCS; placebo vs. tDCS + iBT; tDCS vs. tDCS + iBT). Sample size per arm was calculated based on the smallest detectable group difference (EStdcs vs. combination = -0.4, ESplacebo vs. tdcs = -0.4). Significance levels were Bonferroni corrected for 3-way pairwise comparisons ($\alpha = 0.05/3$) to control family-wise error rate, while still allowing for more anti-conservative adjustment in the final analysis 170–172. Dropouts were assumed to be monotonically increasing (Weibull) and equally distributed between treatment arms. We obtained a total N of 210 participants assuming 10% attrition rate (70 per arm).

Attrition: Missing data will be handled using an intention-to-treat (ITT) approach.

Statistical analysis: Results will be considered statistically significant if a two-sided $p<0.05$ is obtained. Primary outcome: Linear hierarchical model analysis using a first order regressive covariance structure, which includes all observed variables without the need of inputting missing data. The dependent variable is HDRS-17, independent variables are time (all observations until week 6) and group (placebo, tDCS-only and tDCS+iBT). We will test the statistical significance between the slopes of tDCS + iBT vs. tDCS-only per our primary hypothesis. Secondary outcomes: The same linear hierarchical models will be used for all continuous secondary outcomes. Response and remission are respectively defined as a clinical improvement of symptoms ≥ 50% (response) and a HDRS-17 score ≤ 7 (remission). Binary outcomes will be modeled using mixed logistic regression at each timepoint. Exploratory outcomes:We will investigate predictors of response by testing the interaction of each predictor with the group. Improvement in other depressive domains will be evaluated using the same linear hierarchical models described.

Final Statistical Analysis Plan

Sample size calculation

A sample size of 210 participants, 70 per group, was estimated. The sample size calculation was based on the following assumptions: (1) Baseline HDRS-17 scores and standard deviation (SD) of 25 ±5; (2) monotonically increasing dropouts (Weibull), equally distributed between groups, with an overall attrition rate of 10%; (2) placebo effects in the double-sham group equal to 1 effect size (ES, calculated as difference in mean change divided by SD); (3) the "ptES-only" arm will have the same placebo effects present in the double-sham arm (ES = 1), plus a treatment response of ES = 0.4; and, (4) the "double-active" arm will have placebo effects (ES = 1) plus a larger response of ES = 0.8. ES were chosen based on results from previous trials, expecting small to moderate ES for tDCS and for the digital intervention. Sample size per group was estimated based on the smallest detectable group difference (ES tDCS vs. combination = -0.4, ES sham vs. tDCS = -0.4) to achieve a power of 80%, while applying Bonferroni correction to the 3-way pairwise comparisons between groups ($\alpha = 0.05/3$).

Statistical analyses

The intention-to-treat sample was used for data analyses, which were conducted in R version 4.2.2. For the main analysis of the primary outcome (HDRS-17) and other psychiatric scales (BDI, MADRS, CGI-S, HAM-A, PANAS, STAI), a 2-level linear mixed-effects regression model (LMM) was set up with the continuous scale score as outcome, assuming a linear relationship over time. LMMs included a discrete factor for treatment group, a continuous time factor over 5 time points (baseline and weeks 2, 3, 4, and 6) and

their interaction as fixed effects, and patient as random effect. Regarding the random effect patient, for each outcome, a «complete» model with patient-specific random intercept and slope and a "sparse" model with patient-specific random intercept only were fitted. The complete and the sparse models were compared with a likelihood-ratio-test (LRT). A significant LRT indicated that model fit was better with the random slope included and thus the complete model was retained. In absence of significance, the sparse model with random intercept only was selected. The selected model was then used to investigate the fixed effects, with the interaction of time and group probing for treatment effects across time. Significance of model factors was determined using Type III ANOVA with Satterthwaite approximation to degrees of freedom. In the preregistration, we had defined three contrasts to perform pairwise group comparisons over time and mentioned that Bonferroni correction would be applied to these three tests to control for false-positive findings. These contrasts for every outcome can be found in the supplement. Because of the lack of significant findings, we opted to report uncorrected p-values.

Further analyses included the evaluation of response and remission rates for HDRS-17 at endpoint. Response was defined as a reduction by at least half of the score from baseline to endpoint, and remission as an endpoint score smaller or equal to 7. Logistic regression models were employed with endpoint HDRS-17 response or remission as outcome and group as predictor. Regarding usability of the tDCS devices, scores of the five visual analog scale (VAS) items were compared between groups using analyses of variance (ANOVA) for each week separately. In addition, mean scores of the VAS items per subject and week were summarized in five categories (Strongly Disagree (0-19), Disagree (20-39), Neither Agree nor Disagree (40-59), Agree (60-79), Strongly Agree (80-100)) and compared between groups using χ-squared tests or Fisher's exact tests. The latter was employed if

any cell count was five or lower (Table S18). Adverse events for which participants reported that they were at least remotely associated with the intervention were analyzed in three ways. Firstly, we counted how many participants reported at least one mild, moderate, severe, or no adverse event at endpoint and compared the sums between groups using chi-square or Fisher's exact test, as appropriate. Secondly, mild, moderate, and severe occurrences at endpoint were counted for each adverse event separately and compared between groups using chi-square or Fisher's exact test, as appropriate. Thirdly, the number of occurrences of each adverse event was counted for each week, independently of severity, and compared between groups using chi-square or Fisher's exact test, as appropriate. Reasons for dropouts were counted and compared between groups using Fisher's exact tests. To evaluate blinding, a chi-squared one-sample proportion test was used to test if correct guesses differed from 50%. This test was applied to the whole sample and each group separately, both for participants and raters. Due to dropouts, the group sizes were slightly smaller for the analyses of response and remission, adverse events, and blinding

Summary of changes

	Original Protocol	Published Protocol and present report	Summary of changes
Sample size calculation	Based on previous work 25,26,166, we assumed baseline depression scores and standard deviation (SD) of 25 (± 5) on the Hamilton depression rating scale distributed equally between groups. Placebo effect would impact baseline depression scores in one effect size (ES) in SD units (ES = difference in mean change divided by SD). TDCS monotherapy would have a response of ES = 0.4 when compared to placebo and the combination of tDCS and iBT would have a larger response of ES = 0.8 when compared to placebo. Therefore, endpoint scores of 20, 18 and 16 were used. Total sample size (N) was determined to adequately power ($1-\beta = 0.8$) statistical tests for differences in change over 4 measurements (continuous linear change) between treatment arms (time x group interaction) in the framework of linear hierarchical models (LMM). 167,168 Following CONSORT-guideline extensions for the planning of multi-arm parallel-group randomized trials 169, power was not calculated for a global test of significance (e.g. global F-test) but for all combinations of planned pairwise comparisons (placebo vs. tDCS; placebo vs. tDCS + iBT; tDCS vs. tDCS + iBT). Sample size per arm was calculated based on the smallest detectable group difference (EStdcs vs. combination = -0.4, ESplacebo vs. tdcs = -0.4). Significance levels were Bonferroni corrected for 3-way pairwise comparisons ($\alpha = 0.05/3$) to control family-wise error rate, while still allowing for more anti-conservative	A sample size of 210 participants, 70 per group, was estimated. The sample size calculation was based on the following assumptions: (1) Baseline HDRS-17 scores and standard deviation (SD) of 25 ±5; (2) monotonically increasing dropouts (Weibull), equally distributed between groups, with an overall attrition rate of 10%; (2) placebo effects in the double-sham group equal to 1 effect size (ES, calculated as difference in mean change divided by SD); (3) the "ptES-only" arm will have the same placebo effects present in the double-sham arm (ES = 1), plus a treatment response of ES = 0.4; and, (4) the "double-active" arm will have placebo effects (ES = 1) plus a larger response of ES = 0.8. ES were chosen based on results from previous trials, expecting small to moderate ES for tDCS and for the digital intervention. Sample size per group was estimated based on the smallest detectable group difference (ES tDCS vs. combination = -0.4, ES sham vs. tDCS = -0.4) to achieve a power of 80%, while applying Bonferroni correction to the 3-way pairwise comparisons between groups (α	No changes

	adjustment in the final analysis 170–172. Dropouts were assumed to be monotonically increasing (Weibull) and equally distributed between treatment arms. We obtained a total N of 210 participants assuming 10% attrition rate (70 per arm).	= 0.05/3).	
Statistical Analysis	*Primary outcome*: Linear hierarchical model analysis using a first order regressive covariance structure, which includes all observed variables without the need of inputting missing data. The dependent variable is HDRS-17, independent variables are time (all observations until week 6) and group (placebo, tDCS-only and tDCS+iBT). We will test the statistical significance between the slopes of tDCS + iBT vs. tDCS-only per our primary hypothesis. *Secondary outcomes:* The same linear hierarchical models will be used for all continuous secondary outcomes. Response and remission are respectively defined as a clinical improvement of symptoms ≥ 50% (response) and a HDRS-17 score ≤ 7 (remission). Binary outcomes will be modeled using mixed logistic regression at each timepoint.	For the main analysis of the primary outcome (HDRS-17) and other psychiatric scales (BDI, MADRS, CGI-S, HAM-A, PANAS, STAI), a 2-level linear mixed-effects regression model (LMM) was set up with the continuous scale score as outcome, assuming a linear relationship over time. LMMs included a discrete factor for treatment group, a continuous time factor over 5 time points (baseline and weeks 2, 3, 4, and 6) and their interaction as fixed effects, and patient as random effect. Regarding the random effect patient, for each outcome, a «complete» model with patient-specific random intercept and slope and a "sparse" model with patient-specific random intercept only were fitted. The complete and the sparse models were compared with a likelihood-ratio-test (LRT, see Table S5). A significant LRT indicated that model fit was better with the random slope included and thus the complete model was retained. In absence of significance, the sparse model with random intercept only was selected. The selected model was then used to investigate the fixed effects, with the interaction of time and group probing for	We did not apply Bonferroni correction to P-values because there were no significant findings. For brevity's sake, the results section in the main manuscript focuses on the overall F-test for the interaction of group and time, while the group contrasts defined in the original protocol can be found in the supplement. The present report is more detailed regarding variables and model selection.

		treatment effects across time. Significance of model factors was determined using Type III ANOVA with Satterthwaite approximation to degrees of freedom. In the preregistration, we had defined three contrasts to perform pairwise group comparisons over time and also mentioned that Bonferroni correction would be applied to these three tests to control for false-positive findings. These contrasts for every outcome can be found in the supplement (Table S4). Because of the lack of significant findings, we opted to report uncorrected p-values.	