

Feasibility of Computerized Cognitive-Behavioral Therapy Combined With Bifrontal Transcranial Direct Current Stimulation for Treatment of Major Depression

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Background: Cognitive behavioral therapy (CBT) is effective in the treatment of major depressive disorder (MDD). Transcranial Direct Current Stimulation (tDCS) has demonstrated preliminary antidepressant effects and beneficial effects on cognitive function.

Objective: We investigated the feasibility and acceptability of using tDCS to enhance the effects of computer-based CBT for treatment of MDD.

Materials and Methods: In a randomized, double-blind, sham-controlled study, 14 patients with MDD on stable or no pharmacotherapy received active or sham bifrontal tDCS for four weeks with concurrent CBT.

Results: Ten participants completed the protocol. Three withdrew from the study because of lack of efficacy or dislike of the eCBT program. One was discontinued from the protocol by the investigators. Treatment was well tolerated, and most side-effects were mild and consistent with prior tDCS research. Pooled data from both groups showed significant baseline to endpoint improvement in depression ($p = 0.008$). Overall percent change on the HAM-D-21 was 28.98%. The study was underpowered to detect differences in tDCS treatment groups.

Conclusions: Combining tDCS with computer-based CBT is feasible for MDD. Further work is needed to evaluate potential synergistic effects of combined tDCS and CBT.

Keywords: Depression, transcranial direct current stimulation, cognitive behavior therapy

Conflict of Interest: The authors reported no conflict of interest.

INTRODUCTION

Major depressive disorder (MDD) remains a common and inadequately treated illness. There is a pressing need to devise novel, easily accessible, and more effective antidepressant strategies. Several studies support the clinical use of transcranial direct current stimulation (tDCS) as a therapy for MDD (1–5). Furthermore, tDCS has been shown to enhance cognitive functions such as working memory (2,6,7). Cognitive behavioral therapy (CBT) is an evidence-based psychotherapy for MDD (8,9), which maintains efficacy when presented in a computerized form (electronic CBT, or eCBT) (10–12). Recently, the combination of tDCS with CBT has been proposed, suggesting interactive effects of both methodologies on cognitive functions such as top-down emotional control (13). These effects, the possible enhancement by tDCS of working memory during CBT, and the antidepressant effects of the both therapies separately make a combined treatment protocol an intriguing possibility. Here, we present the first systematic research on this promising combined approach. As it is uncertain what effects the timing of stimulation relative to other treatments has on outcomes (6,14), we investigated the feasibility, acceptability, and potential antidepressant effect of bifrontal tDCS concurrent with eCBT, to inform the design of a larger clinical trial to treat depression.

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METHODS

Participants

Patients with current primary MDD were recruited through flyers and clinician referrals. Study enrollment required a Hamilton depression rating scale (HAM-D-28) (15) score ≥ 18 and a stable psychotropic regimen (or no psychiatric medications) for at least six weeks prior to screening. Specific exclusion criteria included a lifetime history of bipolar, psychotic, or obsessive-compulsive disorder, lifetime history of head injury with loss of consciousness, significant neurological disorders, pregnancy, breastfeeding, or prior exposure to tDCS or formal CBT. The study was carried out in accordance with the Declaration of Helsinki and written consent was obtained on forms approved by the Institutional Review Boards of Butler Hospital and Beth Israel Deaconess Medical Center.

Assessments

MDD was diagnosed with the Mini International Neuropsychiatric Interview (16). Depression severity was assessed with the HAM-D-21, and by self-report on the Inventory of Depressive Symptomatology (IDSSR) (17) and the Patient Health Questionnaire (PHQ-9) (18). Global illness severity (baseline and endpoint) and clinical change at endpoint were assessed with the clinical global impressions (CGI) scales (19). Adverse events were assessed by a standard questionnaire following each treatment session (20). Participants were asked to rate ten adverse events associated with tDCS on a scale from 1 to 4 (1 = absent, 2 = mild, 3 = moderate, and 4 = severe). The questionnaire also contained an "other" category to narratively capture other emergent events. In addition, participants were instructed to spontaneously report the presence and intensity of any potential adverse events at any time.

Study Design

Participants were randomly assigned to receive 12 sessions (three days per week for four weeks) of active or sham tDCS administered concurrently with 12 modules of CBT delivered via computer-based modules. This design was chosen for several reasons, including matching both prior tDCS studies and clinical CBT delivery. First, while some studies investigating tDCS and depression have used a five sessions per week protocol, others used a three sessions per week protocol (21,22). Furthermore, the standard frequency of CBT sessions is approximately twice weekly (23). Additionally, because this was a feasibility study, we selected a visit frequency that we felt would be achievable for our depressed participants. In line with our design, a recent study combining rTMS with CBT used a protocol allowing a treatment frequency ranging from two to three sessions per week to twice a day, as determined by the therapist and participant (24). HAM-D-21 was administered at baseline and within 72 hours of the last treatment session, and self-report scales were administered at sessions 3, 6, and 9. Subjects and raters were blinded to treatment group but tDCS technicians were unblinded. At completion or withdrawal from the study, participants and raters were asked to guess whether they had received active or sham tDCS, to rate how certain they were of their guess, and to provide what rationale informed their guess.

eCBT

CBT was delivered using modified modules of the eCBT software Good Days Ahead (Empower Interactive, Moraga, CA, USA). Modules involved watching a series of videos, reading text, and typing in responses to module-specific exercises presented on the computer screen. Activities and skills included identifying negative thoughts, substituting positive thoughts, and activity schedules. Participants met with a trained clinician prior to their first treatment session and after completion or withdrawal from the study. tDCS/eCBT sessions did not involve interaction with a clinician unless the participant experienced an unexpected or severe adverse event, experienced a worsening of psychiatric symptoms, or requested to speak with a clinician. Sessions were fully supervised by a trained technician until both tDCS and eCBT was completed to ensure safety and provide technical support. Study technicians were instructed to be courteous but not to engage with patients in a therapeutic manner. After each session, participants were given printed "homework" pages for practicing the eCBT skills presented in the corresponding module. Time spent on homework, as well as participant feedback, was recorded at the start of each session for the previous session's exercises. Homework was voluntary, and participation was not contingent on its completion.

tDCS+eCBT Sessions

Bifrontal tDCS was delivered using a Chattanooga Ionto device (DJO Global, Guildford Surrey, UK) and 25 cm² sponge electrodes, with the anode over left DLPFC (F3) and the cathode over right DLPFC (F4) informed by Fregni et al. (2). Active tDCS was applied at 2 mA for 30 min with a 2 min ramp-up at the beginning and a 30 sec ramp-down period at the end of stimulation. For sham, the current was ramped up to 2 mA over a 2 min period and then immediately ramped down to off over a 30 sec period. Technicians mimed turning off the tDCS device at the end of 30 min for sham participants to match the experience of active tDCS. The 2-min ramp-up period was chosen after we found that our initial participants were unable to tolerate a quicker (i.e., 30 sec) ramp-up period due to stimulation site discomfort. A 2-min ramp-up allowed all participants to reach 2 mA with tolerable sensations at the stimulation site. The eCBT module was started 5 min after start of stimulation (3 min after the completion of the ramp-up period). Modules were designed to last the majority of the stimulation time (30 min), however, participants navigated through each module at their own pace. If a participant finished the module prior to the completion of the 30-min active/sham tDCS, they were instructed to work on the homework exercises or review module material. The participant was asked not to read any other material or look at their phone to avoid exposure to potentially emotionally salient material during stimulation. If a participant had not yet finished the eCBT module after 30 min of active/sham tDCS, the device was turned off (or mimed) and the participant was allowed to complete the module.

RESULTS AND DISCUSSION

A total of 18 participants consented; 14 met eligibility criteria and received at least one blinded tDCS+eCBT session (Table 1). As a result of screening and randomization procedures, the group sizes were unbalanced with nine assigned to active and five to sham tDCS. Five (55%) active and four (80%) sham participants

Table 1. Participant Clinical Characteristics and Treatment Outcomes.

| Group | Total number of sessions | Sex | Age | Past treatment modalities | Concurrent medications | IDSSR | PHQ9 | HAMD-21 | Adverse events [†] | Disposition | Patient rated improvement |
|-----------|--------------------------|-----|-----|---|---|----------|----------|----------|---|--|---------------------------|
| 1 Active | 9 | F | 34 | Inpatient, IOP, Psychotherapy, ECT, TMS, medication | Citalopram, lurasidone, trazadone, lorazepam, buspirona | 43(2%) | 17(-12%) | 29(45%) | Unpleasant sensations under the electrode, sleepiness | Withdrew consent due to lack of efficacy | No change |
| 2 Active | 4 | F | 64 | Psychotherapy, rTMS, medication | Methylphenidate, SAM-e, zolpidem | 36(0%) | 15(13%) | 12* | Heart palpitations, ankle swelling | Early termination by PI | Not assessed |
| 3 Sham | 6 | F | 58 | Psychotherapy, medication | Bupropion | 38(-5%) | 11(-9%) | 16(0%) | Unpleasant sensations under the electrode | Withdrew consent due to lack of efficacy | No change |
| 4 Active | 7 | F | 62 | Inpatient, IOP, psychotherapy, rTMS, medication | Amphetamine/dextroamphetamine, lorazepam, hydrocodone/acetaminophen | 61(0%) | 24(0%) | 28(0%) | None | Withdrew consent due to lack of efficacy | Minimally worse |
| 5 Sham | 12 | F | 49 | Medication | Citalopram | 36(69%) | 16(69%) | 19(58%) | Unpleasant sensations under the electrode | Completed protocol | Very much improved |
| 6 Sham | 12 | F | 64 | Inpatient, IOP, psychotherapy, medication | Venlafaxine, amphetamine/dextroamphetamine, diazepam | 48(45%) | 15(47%) | 23(39%) | None | Completed protocol | Minimally improved |
| 7 Active | 12 | F | 32 | Inpatient, IOP, psychotherapy, medication | Lamotrigine, bupropion, duloxetine | 38(18%) | 15(40%) | 28(29%) | None | Completed protocol | Minimally improved |
| 8 Sham | 12 | F | 64 | Psychotherapy, medication | Sertraline, bupropion, diphenhydramine | 41(39%) | 16(25%) | 17(35%) | None | Completed protocol | Minimally improved |
| 9 Active | 12 | F | 59 | Psychotherapy, Medication | Sertraline | 21(-10%) | 12(17%) | 10(-10%) | Unpleasant sensations under the electrode, difficulty concentrating | Completed protocol | Minimally improved |
| 10 Active | 7 | F | 44 | Inpatient, psychotherapy, medication | None | 40(3%) | 17(-6%) | 19(-5%) | Unpleasant sensations under the electrode | Withdrew consent due to lack of efficacy /higher level of care | Minimally worse |
| 11 Sham | 12 | M | 67 | Inpatient, psychotherapy, medication | Trazodone, bupropion, duloxetine, amphetamine/dextroamphetamine | 26(15) | 10(20) | 14(29) | Unpleasant sensations under the electrode | Completed protocol | No change |
| 12 Active | 12 | F | 34 | Psychotherapy, medication | Fluoxetine, bupropion | 32(47) | 10(40) | 11(64) | Unpleasant sensations under the electrode, sleepiness, difficulty concentrating | Completed protocol | Much improved |
| 13 Active | 12 | F | 61 | Psychotherapy, medication | Fluoxetine, bupropion | 33(6%) | 19(53%) | 13(23%) | Headache, difficulty concentrating, sleepiness, neck Pain | Completed protocol | Minimally improved |

Table 1. Continued

| Group | Total number of sessions | Sex | Age | Past treatment modalities | Concurrent medications | Baseline score (% change at endpoint) | Adverse events [†] | Disposition | Patient rated improvement |
|-------|--------------------------|-----|-----|---------------------------|--|---|---|--------------------|---------------------------|
| 14 | 12 | M | 53 | Psychotherapy, medication | Amphetamine/dextroamphetamine, lithium | IDSSR 27(0%) PHQ9 14(29%) HAM-D-21 10(-20%) | Unpleasant sensations under the electrode, difficulty concentrating | Completed protocol | Much improved |

*Negative values for % change represent a worsening of symptoms on that measure.

[†]Adverse events rated moderate or severe in nature by the participant. None were serious.

[‡]PI terminated subject following report of heart palpitations, pedal edema, and new information about previously diagnosed cardiac condition (prior to enrollment). Endpoint assessments are missing, so %change could not be calculated. IOP, intensive outpatient program/day hospital; ECT, electroconvulsive therapy; rTMS, repetitive transcranial magnetic stimulation therapy; SAMe, S-adenosyl methionine (nutritional supplement).

completed all the procedures. Length of current depressive episode was not known for all participants. For those who were able to provide that information ($n = 6$), the average length of the current episode was 3.2 years. In regard to participant blinding, the correct condition (active or sham) was guessed by 46% of participants. Significantly more active as compared to sham participants correctly guessed their condition; five out of eight active participants guessed the correct condition while only one sham participant correctly guessed the sham condition ($\chi^2 = 4.064$, $df = 1$, $p < 0.05$), suggesting that our sham protocol was adequate. The blinded condition was correctly guessed by the assessment rater in 50% of the cases.

Three active participants and one sham participant withdrew before completing 12 sessions because of a lack of efficacy and/or dislike of the eCBT program, and one (active) was discontinued due to onset of heart palpitations and ankle swelling that was thought to be unrelated to tDCS. Most participants had either a positive or neutral opinion of the study, demonstrating the general acceptability of the intervention. Negative opinions by two participants were related to the eCBT content. For example, one participant with a long and more severe history of depression expressed that the actor portraying a depressed person in the eCBT program seemed "too healthy" and did not accurately portray the participant's experience or thoughts. Another participant felt that the amount of information presented in each session was overwhelming. These concerns, which could not be addressed with our eCBT, could have been accommodated by a therapist during face-to-face CBT. However, the electronic platform was appreciated by other participants. One, for instance, enjoyed the eCBT because she found it "relaxing to take time by herself to focus on her thoughts." The eCBT platform, with its ease of deliverability, may have been ideally suited for those with less severe depression or with less prior exposure to psychotherapy while not meeting the needs of those with more severe depression or more complicated psychiatric histories. In addition, eCBT can provide a less expensive alternative to traditional face-to-face therapy and may also be useful in areas where access to in-person therapy is limited (12). Finally, eCBT allowed for a standardized treatment protocol against which to investigate the use of concurrent tDCS.

Paired *t*-test of pooled data ($n = 14$) showed significant improvement in mean depression scale scores from baseline to the endpoint on HAM-D-21 (baseline: $M = 17.786$, $SE = 1.825$, endpoint: $M = 13.846$, $SE = 1.728$, $t = 3.156$, $p = 0.008$, $d = 0.603$), IDSSR (baseline: $M = 36.929$, $SE = 2.636$, endpoint: $M = 30.642$, $SE = 3.344$, $t = 2.575$, $p = 0.023$, $d = 0.055$), PHQ-9 (baseline: $M = 15.071$, $SE = 1.003$, endpoint: $M = 11.643$, $SE = 1.428$, $t = 3.212$, $p = 0.007$, $d = 0.743$), CGI improved at a trend level (baseline: $M = 4.46$, $SE = 0.144$, endpoint: $M = 3.667$, $SE = 0.333$, $t = 2.055$, $p = 0.067$, $d = 0.887$) The completer sample ($n = 9$) was too small for statistical comparison of active vs. sham groups. Two participants (one active and one sham) met categorical response criteria ($\geq 50\%$ reduction in score) on all measures and one sham participant met remission criteria on the IDSSR.

Side-effects included mild unpleasant sensations below the electrodes, endorsed by all participants, consistent with those commonly reported in tDCS studies (20); 66% in the active group and 60% in the sham group rated these sensations as moderate or severe in nature. Unpleasant sensations under the electrodes may stem from the intensity of stimulation and the impedance of the system (25). The intensity of stimulation can be manipulated by reducing the current being delivered to the scalp. Reducing the current density by increasing electrode size has been

suggested as one way to decrease intensity. However, studies have shown that larger electrodes are associated with equivalent or more unpleasant sensations than smaller electrodes (26). Additionally, increasing the size of the electrodes, while possibly reducing current density, raises the risk of delivering stimulation to regions of the brain outside of the dLPFC. Issues surrounding impedance may also have factored into participant discomfort. When impedance is high in a tDCS system, it can contribute to unpleasant sensations at the stimulation site (27). While the tDCS systems used in this study had an impedance limit past which the device would not operate, it did not allow technicians to monitor impedance values or set a user-identified impedance limit. The use of a device with these features may reduce the occurrence and severity of unpleasant sensations under the electrodes.

Other adverse events reported were sleepiness (66% active, 40% sham), and headache (55% active, 20% sham). Sleepiness has been previously reported with HD tDCS to the dLPFC (28). Whereas it is possible that tDCS contributes to feelings of sleepiness, depression is often accompanied by fatigue. It is also important to note that participants in both groups reported sleepiness. One of our sham participants attributed her sleepiness during the sessions to the fact that it was the only time during her day that she was able to sit down and rest. Headache has been previously reported during tDCS (20). Possible sources of headache are the stimulation itself, discomfort under the electrodes, the apparatus used to maintain contact between the scalp and electrodes, or, in our study, from reading on a computer screen.

Concentration difficulties were reported exclusively by participants in the active group. In fact, all participants in the active tDCS group and none in the sham group reported difficulty concentrating on content during the eCBT sessions. No participants reported this problem persisting outside of the tDCS+eCBT procedures. Possible explanations include direct neuromodulatory effect of active stimulation on cognitive function or distraction because of unpleasant sensations on the scalp. Mild discomfort and diminished ability to concentrate were not limited to the first few sessions, suggesting that delivery of "offline" tDCS (immediately before or after the eCBT) might have been better tolerated and allowed better focus during eCBT. There remains controversy about whether "online" (stimulation concurrent with cognitive task) tDCS produces superior effect on working memory (6,14).

Of note, our study included CBT homework, which was tracked but not required. All participants reported spending at least some time on homework, with participants spending an average of 0.41 hours on homework exercises between each session. Among participants who completed the protocol, the total amount of time spent on homework over the four-week study was highly variable, ranging from under one-half hour to more than 17 hours. Future studies should investigate whether time spent on homework exercises impacts efficacy outcomes, as is the case for standard CBT (29).

Whereas our study was underpowered to detect differences in efficacy between groups, several studies of tDCS for the treatment of depression have shown significant improvement in symptoms in the active tDCS group as compared to sham (1–5). However, a recently published study by Loo et al. investigated tDCS alone as a treatment for MDD (5). Counter to prior reports, they found more patients met remission criteria in the sham tDCS group than in the active tDCS group, raising the question of whether there were previously unknown counter-therapeutic effects of active tDCS. Other possible interpretations of the negative results of that controlled trial concern the question of the optimal dose of tDCS

for treating MDD and potential biologically active effects of brief or low-intensity current delivered during sham stimulation.

The limitations of this pilot study are those inherent to small feasibility studies. However, these preliminary results suggest that tDCS enhancement of eCBT merits further evaluation in a larger trial for development of a potentially novel treatment for major depression. Future studies must achieve suitable participant tolerability to decrease the drop-out rate and allow focus on the CBT skills provided in the modules. We believe that by addressing the side-effects and participant feedback discussed in this study, achieving such tolerability will be possible. Factors to consider in the design of future studies include selection of an appropriate tDCS device with built-in impedance controls, improving participant response to the eCBT program, increasing participant comfort during stimulation and/or delivering tDCS and eCBT separately, and considering engagement with homework in relation to efficacy.

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Authorship Statements

Drs. Carpenter, Philip, Weigand, Press, Tyrka, and Ms. Welch designed the study, interpreted data, and contributed to drafting the manuscript. Dr. Carpenter, Dr. Press, Ms. Welch, and Ms. Hooker conducted the study, including patient recruitment, administration of stimulation procedures, and data collection. All authors had complete access to the study data, contributed to, and approved the final manuscript.

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