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Study design and methodology for a multicentre, randomised controlled trial of transcranial direct current stimulation as a treatment for unipolar and bipolar depression

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ABSTRACT

Transcranial Direct Current Stimulation (tDCS) is a new, non-invasive neuromodulation approach for treating depression that has shown promising efficacy. The aim of this trial was to conduct the first international, multicentre randomised controlled trial of tDCS as a treatment for unipolar and bipolar depression. The study recruited 120 participants across 6 sites in the USA and Australia. Participants received active or sham tDCS (2.5 mA, 20 sessions of 30 min duration over 4 weeks), followed by a 4-week open label active treatment phase and a 4-week taper phase. Mood and neuropsychological outcomes were assessed with the primary antidepressant outcome measure being the Montgomery-Asberg Depression Rating Scale (MADRS). A neuropsychological battery was administered to assess safety and examine cognitive effects. The study also investigated the possible influence of genetic polymorphisms on outcomes. The trial was triple-blinded. Participants, tDCS treaters and study raters were blinded to each participant's tDCS group allocation in the sham-controlled phase. Specific aspects of tDCS administration, device operation and group allocation were designed to optimise the integrity of blinding. Outcome measures will be tested using a mixed effects repeated measures analysis with the primary factors being Time as a repeated measure, tDCS condition (sham or active) and Diagnosis (unipolar or bipolar). A restricted number of random and fixed factors will be included as required to account for extraneous differences. As a promising treatment, tDCS has excellent potential for translation into widespread clinical use, being cost effective, portable, easy to operate and well tolerated.

1. Introduction

Despite improvements in quality of health worldwide, the burden from mental health disorders is rising along with a shift in burden of disease from premature death to years lived with disability (YLDs) [34]. Major depressive disorder is the second leading cause of YLDs and despite treatment advancements, prevalence has not declined in the past two decades [55].

The development of non-convulsive brain stimulation therapies such as transcranial Direct Current Stimulation (tDCS) holds great promise in offering an alternative, new class of treatments that are non-invasive and well tolerated [40,42]. tDCS involves applying a low intensity, sustained electrical current between anodal and cathodal electrodes placed on the scalp, which passes through to underlying brain regions and modulates brain activity. tDCS results in shifts in the resting membrane potential with anodal stimulation resulting in increased neuronal excitability and cathodal stimulation resulting in hyperpolarisation and decreased excitability [6].

Clinical trials of tDCS for depression have typically applied anodal stimulation to the left dorsolateral prefrontal cortex (DLPFC) with the cathode placed over the contralateral cortex (usually F4 or F8 on the 10-20 EEG system). The majority of meta-analyses of randomised, controlled trials (RCTs) of tDCS have found that tDCS is superior to sham stimulation [9,25,30,50] with the effect size (*B* coefficient = 0.35) of

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tDCS being comparable to that of repetitive transcranial magnetic stimulation (rTMS) and antidepressant medication in primary care [9]. However, the proportion of responders remains suboptimal and while higher tDCS parameters appear to be positively associated with tDCS efficacy [9], optimal stimulation parameters have yet to be sufficiently defined.

In addition, there has been no RCT specifically examining tDCS in bipolar patients. Published evidence in bipolar participants consists of only 15 participants from RCTs (N = 8 [27]; N = 2 [37]; N = 5 [38]) but notably, a recent meta-analysis of RCTs found bipolar depression to be a significant predictor of improvement in depressive symptoms after a course of tDCS [9] although the percentage of bipolar participants was low (3.8%) and half of the RCTs included did not recruit bipolar participants.

Thus, while there is growing evidence that tDCS may have acute and sustained efficacy in both unipolar and bipolar depression, further research is needed to: 1) examine and optimise stimulation parameters; 2) provide more substantive evidence of efficacy and safety by comparing active versus sham tDCS over a longer treatment period and in a larger cohort recruited across multiple study sites to improve generalizability; 3) explore the efficacy of tDCS in a larger bipolar sample and examine any potential differences in outcome measures compared to unipolar depression; 4) examine potential cognitive benefits of tDCS using a targeted neuropsychological battery; and 5) to explore potential genetic predictors of response to tDCS.

2. Design and methods

2.1. Participants

The sample includes participants recruited at 1 study site in Australia (University of New South Wales) and 5 in the USA (Duke University School of Medicine, Durham, NC; Emory University, Atlanta, GA; Rowan University, Cherry Hill, NJ; Sheppard Pratt Health System, Baltimore, MD; and University of Texas Southwestern Medical Center, Dallas, TX.)

At study entry, participants were at least 18 years old, were in a current major depressive episode of minimum 4-week duration and defined according to Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) criteria [2], and had a score of at least 20 on the Montgomery-Asberg Depression Rating Scale (MADRS; [32]). The DSM-IV-TR diagnoses were established using the Mini International Neuropsychiatric Interview (MINI; Version 5.0.0 [49]). Exclusion criteria included: a current major depressive episode of >3 years duration; failure of >3 adequate antidepressant trials in the current episode; DSM-IV-TR psychotic disorder; drug or alcohol abuse or dependence in the preceding 3 months before study entry; inadequate response to ECT in the current major depressive episode; rapid clinical response required (e.g., due to high suicide risk); clinically defined neurological disorder or insult; metal in the cranium, skull defects, or skin lesions on the scalp (e.g., cuts, abrasions, rash) at proposed tDCS electrode sites; and pregnancy.

Participants were free of antidepressant medications or continued on stable doses of antidepressant medications to which they had failed to respond after an adequate course of treatment, with dosage unchanged for at least four weeks prior to study entry. Bipolar participants were on a mood stabiliser medication as prophylaxis against treatment-emergent mania [8,20]. Long acting benzodiazepines were not permitted during the study, though participants were permitted to take lorazepam (up to 2 mg daily but not within 8 h prior to tDCS stimulation).

Based on an effect size of 0.74 derived from a meta-analysis of all available RCTs of tDCS up to 2012 [25], and assuming that 1) tDCS at the higher stimulation parameters used in this study would be at least as effective as the stimulation parameters used in these earlier RCTs and 2) the efficacy in bipolar depression would be at least comparable to that in unipolar depression, a sample of 30 participants per group would be required to demonstrate a significant difference between active and sham tDCS (at 80% power and $\alpha = 0.05$). Thus, the planned study sample was 60 unipolar and 60 bipolar participants with allocation to the active and sham conditions equally divided for each diagnostic group. Assuming an attrition rate of 5%, up to 126 participants in total could be recruited in order to attain a sample of 120 participants with at least one post baseline rating.

2.2. Design

The main study phase of 4 weeks duration used a triple-blinded, parallel, randomised, sham-controlled design. Blinding was maintained until the study was completed and the dataset locked. Participants were required to attend a total of 20 tDCS sessions conducted on consecutive weekdays over this 4-week period. Participants were randomly assigned by a computer-generated random number sequence to one of 2 groups: active tDCS or sham tDCS. Permuted-block randomisation was used to assign participants to the treatment group such that equal numbers were assigned to active and sham treatment within each block. Randomization was stratified according to whether participants were diagnosed with unipolar or bipolar depression.

After the initial blinded, sham-controlled phase, participants who did not meet the criterion for remission (MADRS score < 10) were offered further treatment in an open label phase that consisted of 20 active tDCS sessions also conducted on consecutive weekdays over 4 weeks.

Participants who completed 4 or more weeks of daily tDCS treatments were eligible to enter a taper phase. The taper phase consisted of 4 additional tDCS treatments provided on a weekly basis with the final taper session coinciding with a 1 month follow-up visit. Participants, who experienced a remission in depressive symptoms by the end of the sham-controlled phase, directly entered the taper phase without undergoing the open label phase. These participants received the same treatment allocation as during the sham-controlled phase. Participants completed a final follow-up visit 3 months after trial completion. Participants remained blinded to their tDCS group allocation in the sham-controlled phase for the duration of the study, including the taper phase. Mood and neuropsychological function were assessed at the intervals shown in the Study Design Diagram (see Table 1).

A participant could be withdrawn from the study if: a serious adverse event occurred; a site investigator believed that for safety reasons, it was in the best interest of the participant to be withdrawn; the participant missed ≥3 consecutive tDCS sessions in the sham-controlled or open label phase; the participant missed a total of ≥6 out of 20 tDCS sessions in the sham-controlled or open label phase; the participant became hypomanic or manic; pregnancy occurred.

2.3. Materials and procedures

2.3.1. tDCS

tDCS was applied via two 7 cm × 5 cm saline-soaked sponge-covered electrodes held in position by a headband customised for the electrode montage used. The headband was designed to evenly secure the sponge surface to the scalp at the required coordinates, maintain electrode orientation, and allow inspection of sponge-skin contact quality and adjustment if indicated (see below). Stimulation parameters for active tDCS were 30 min per session at 2.5 mA with 30 s ramp up and 30 s ramp down. The anode was centred over the left dorsolateral prefrontal cortex at F3 (10/20 EEG system) and the cathode over the lateral right frontal area at F8 (see Fig. 1).

For sham stimulation, the current was rapidly ramped up to 1 mA over the first 10 s and slowly ramped down over the next minute to allow participants to feel typical initial sensations of active tDCS (e.g., tingling, itching at the electrode sites) while minimising any potential neuromodulatory effects. To further enhance participant and investigator blinding, tDCS devices were programmed such that participants in the sham group were randomly allocated to experience a steady ramp

Table 1
Schedule of outcome measures.

Phase		4-Week sham controlled phase				4-Week open label (active) treatment				Taper phase				Follow-up
Week	Wk 0 (Baseline)	Wk 1	Wk 2	Wk 3	Wk 4	Wk 1	Wk 2	Wk 3	Wk 4	Wk 1	Wk 2	Wk 3	Wk 4 / 1 M	3 M
Session	Pre 1	1–5	6–10	11–15	16–20	21–25	26–30	31–35	36–40	41	42	43	44	
Mood/quality of life assessments														
MADRS	X		X		X		X		X				X	X
CGI-S	X													
CGI-I			X		X		X		X				X	X
QIDS-SR	X	X	X	X	X	X	X	X	X	X	X	X	X	X
YMRS	X		X		X		X		X				X	X
Altman	X	X	X	X	X	X	X	X	X	X	X	X	X	X
QoL	X				X				X				X	X
Neuropsychological assessments														
MoCA	X				X				X					
CVLT-II	X				X				X					
Ruff 2 & 7	X				X				X					
WAIS-IV Digit Span	X				X				X					
SDMT	X				X				X					
D-KEFS Verbal Fluency	X				X				X					
WTAR	X													
Cognitive Failures Questionnaire	X				X				X					

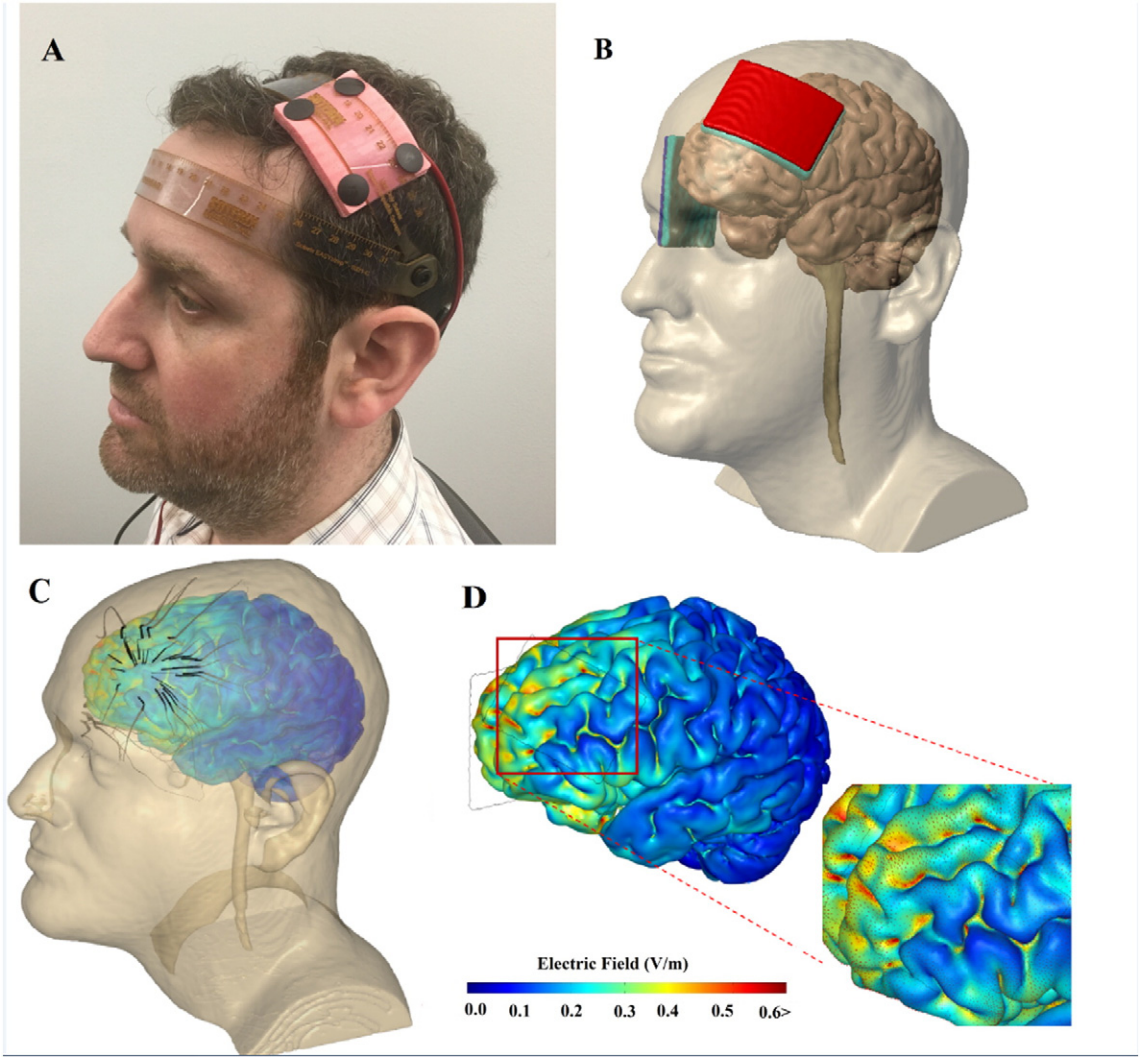

Fig. 1. tDCS montage used in the multicentre, randomised controlled trial of tDCS for the treatment of unipolar and bipolar Depression. A) After identifying 10/10 electrode locations (F3, F8), 5 × 7 cm sponge-encased electrodes were secured to the participant's head using a customised headgear. B) A MRI-derived head model of the head was adapted [14], and anode (red) and cathode (black) electrode positioning reproduced. C) Following established computational modelling workflow [5,54], finite-element-method (FEM) stimulations predict current flow across the head (black flux lines) during tDCS and resulting electric fields at the cortex (false colour). D) Detailed view of cortical electric fields with inset around DLPFC target.

up and down to 0.5 mA over 1 min at either 10 min or 20 min into the session to elicit faint scalp sensations during the session that would nonetheless still be unlikely to produce lasting changes in cortical excitability [36]. tDCS operators across all sites underwent initial training (via in-person demonstration at the initial study investigator meeting followed by study-site in-person demonstration and televideo presentations) conducted by the co-ordinating site (UNSW) with a staff member from the co-ordinating site observing via video link the first three tDCS sessions conducted by each operator at each study site as part of the credentialing process.

2.3.2. Assessments and measures

The primary outcome measure for comparing active and sham tDCS over the sham-controlled phase was the MADRS [32] administered by trained raters with established inter-rater reliability (intraclass correlation coefficient > 0.7). Secondary measures were the Clinician Global Impression – Severity of Illness and Clinician Global Impression – Improvement (CGI; Guy, 1976), self-report Quick Inventory of Depressive Symptomatology (QIDS-SR; [45]) and Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form (QLESQ-SF; [18]). The Young Mania Rating Scale (YMRS; [59]) and Altman Self Rating Mania Scale [1] were used to assess for hypomanic and manic symptoms.

The following neuropsychological battery was administered by research staff trained by two clinical neuropsychologists (S.M.M. and D.M.), and was selected to comprehensively assess cognitive function. The neuropsychological battery included the following instruments: Montreal Cognitive Assessment (MoCA; [35]) – global cognitive function; California Verbal Learning Test-II (CVLT-II; [16]) – verbal learning and memory; Ruff 2 & 7 [43] – attention processes; Wechsler Adult Intelligence Scale-IV edition (WAIS-IV) Digit Span subtest; [58]) – simple auditory attention and working memory; Symbol Digit Modality Test (SDMT; [51]) – psychomotor processing speed; Delis-Kaplan Executive Function System (D-KEFS) Verbal Fluency test; [15] – phonemic fluency, semantic fluency, cognitive flexibility; Cognitive Failures Questionnaire [7] – subjective cognitive functioning; and Wechsler Test of Adult Reading (WTAR; [57]) – premorbid intellectual ability. Rating scales and the neuropsychological battery were administered at specified time points (see Table 1). A saliva sample was collected from participants to allow later isolation of DNA for genetic analysis of possible predictors of response to tDCS. Samples were collected through a spit tube and stabilised via solution at room temperature until processing at the end of the study.

2.3.3. Blinding and tDCS device design

The trial is "triple-blinded"; that is, all participants, tDCS treaters and study raters were blinded to each participant's tDCS group allocation in the sham-controlled phase. Specific aspects of tDCS administration, device operation and group allocation were designed to optimise the integrity of blinding. Raters did not administer any tDCS sessions nor were they present in the room during the tDCS sessions. Participants were instructed at the outset of the trial to not discuss any perceived side effects of tDCS with the study rater. To maintain blinding for tDCS treaters, each participant who entered the study was assigned a unique 6-digit ID before the first tDCS session from a predetermined list issued to each study site. A customised tDCS device was developed specifically for the trial whereby ID numbers were pre-programmed into each tDCS device to administer either active or sham tDCS when the number was entered by the tDCS treater. A master list identifying ID numbers with the corresponding tDCS condition was kept only by a study statistician and the tDCS device manufacturers with the coding not to be disclosed to study investigators until the end of the trial or unless required in a medical emergency. The research staff member analysing the final study data was to also be blinded to the tDCS condition when conducting the planned statistical analyses.

In addition to the pre-programmed coding, other aspects of the tDCS device design have been customised to preserve blinding. As outlined above, tDCS devices were programmed to administer two short, ramp up/down periods of relatively low current intensity during sham stimulation to allow participants to feel typical tDCS scalp sensations. During the tDCS session, the device never displayed the current intensity being administered, but only time remaining and a categorical indication of impedance between the electrodes and scalp through a "contact quality" readout of either "optimal", "moderate" or "poor". Indication of just a categorical contact quality, as opposed to dynamic impedance during stimulation, reduces risk of unblinding due to characteristic changes in impedance only during the active arm [24]. Categorical "contact quality" also allows for sham-specific quality scores (see below). Moreover, the contact quality was calibrated to specific impedance changes expected for this trial protocol (electrode design, electrode position, stimulus waveform) and categorical feedback facilitates a clear study protocol decision in response to impedance changes (e.g., as opposed to ambiguity about what impedance is not ideal and actionable before or during a session). tDCS treaters were trained to make adjustments to improve electrode contact quality during the session (e.g., adding saline, tightening the headband) if such quality was moderate or poor, which can sometimes occur during active tDCS. However, tDCS treaters were unaware that the tDCS devices were programmed to provide a readout of moderate or poor contact quality for some sham tDCS sessions so as to make the device readouts indistinguishable between active and sham tDCS.

tDCS devices included a feature that allows stimulation to continue when stimulator output approaches the voltage limit (e.g., due to high impedance) by automatically lowering the current intensity to 2 mA. This unique feature has since been explicitly integrated into other tDCS trial designs [10]. tDCS devices without this function cut off abruptly when the voltage limit is exceeded, potentially unblinding both treaters, who can see stimulation has stopped, and participants, who typically experience transient lightheadedness/dizziness and/or see a phosphene flash when the current is not gradually ramped down. tDCS devices also included a "pause" feature, which could be activated by the treater to transiently decrease the current to zero (or for the sham arm to simulate a ramp down). After any needed adjustments, the stimulation could be reinitiated by the treater. The activation of automatic voltage-limiting features or manual pause events were recorded by the device using a blinded code.

Adequacy of blinding was assessed at the end of the sham-controlled and open label phases by asking participants and raters to guess the tDCS condition administered during the sham-controlled phase. In addition, participants were asked to guess their tDCS condition after the first tDCS session to examine the accuracy of their initial impression and whether this may predict the degree of any subsequent improvement.

2.3.4. Statistical analyses

Active and sham treatment groups will be tested for any differences at baseline in participant demographics as well as depression and treatment indices using chi-square tests for categorical variables or analysis of variance (ANOVA) for continuous variables. Statistical tests will be two-tailed.

Depression ratings and neuropsychological test scores will be analysed for change over the sham-controlled phase using a mixed effects repeated measures (MERM) analysis with Time (assessment time points) as a repeated factor and two between-subjects factors – tDCS condition (active or sham) and Diagnostic Group (bipolar or unipolar). MERM models have been previously recommended for clinical trials as they can better account for individual participant variability in repeated measurements over time and more appropriately handle missing data relative to more traditional repeated measures analytical methods [23]. In addition to testing these three main effects, interactions between tDCS condition and Time, and tDCS condition, Time and Diagnostic Group will also be tested to investigate whether any differences in improvement between active and sham groups will differ

between unipolar and bipolar participants. Study site and participants will be entered as random effects. A restricted number of covariates will be entered if required to correct for baseline imbalances or to better model outcome. Analyses of neuropsychological outcomes will control for change in mood, demographic factors (e.g., age, education) and premorbid intellectual ability (based on the WTAR).

The number of responders (defined as a reduction in MADRS score of ≥50% from baseline) and remitters (defined as a final MADRS score < 10) after 4 weeks of treatment will be compared between groups using a chi-square test. The association between participant or rater guesses (active or sham) and the participant's assigned tDCS condition (active or sham) will also be tested with a chi-square test.

2.3.5. Status of the study

The study was registered with the ClinicalTrials.gov website (Identifier: NCT01562184) on March 21, 2012. The study was approved by the relevant Human Research Ethics Committee/Institutional Review Board for each study site. Recruitment was conducted between July 2012 and August 2015 with the last participant completing the last follow-up visit in November 2015. Due to slow recruitment of bipolar participants, the target sample size was adapted such that recruitment of unipolar participants was permitted to resume following a 4-month stoppage in recruitment after the original target of 60 had been reached while recruitment of bipolar participants remained ongoing throughout the course of the study.

3. Discussion

This trial is the first international, multicentre, sham-controlled RCT of tDCS in depressed patients and the first to formally compare the efficacy of tDCS in unipolar and bipolar depression in a RCT. In administering tDCS on consecutive weekdays from 4 to 8 weeks at 2.5 mA and 30 min per session, tDCS was applied at doses greater than any previous trial. This dose was adapted from prior RCTs [27] but this trial did not include a dose response component. Although there are currently no definitive optimal parameters for tDCS nor any conclusive findings that applying higher doses will have greater therapeutic effects, there is preliminary evidence nonetheless that increasing the frequency, duration and/or current intensity of tDCS may confer greater efficacy. For example, Loo and colleagues increased tDCS parameters of 1 mA given for 20 min every second day for 5 sessions in one study [28] to 2 mA tDCS for 20 min for 15 sessions on consecutive weekdays [27] and found significantly greater improvement in depressive symptoms in participants who received active tDCS compared to those who received sham only in the latter study. In addition, results from a recent meta-analysis suggested that higher tDCS doses may result in improved efficacy [9], although the investigators were unable to specify whether a combination of parameters (e.g., session duration, number of sessions, current intensity, current density) or only a subset of parameters were the primary determinants of efficacy.

Being the first comprehensive trial of tDCS for bipolar depression, this study will also provide the strongest evidence to date as to the efficacy and safety of tDCS in treating bipolar depression. As noted earlier, there is preliminary evidence from a meta-analysis of RCTs that tDCS may be more effective for bipolar depression compared to unipolar depression [9]. In addition, available data from an open label study also suggests that tDCS may be at least as effective in bipolar depression as it is in unipolar depression [8]. Brunoni et al. [8] analysed the results of 14 participants with bipolar depression compared to 17 participants with unipolar depression in an open-label trial that comprised 10 tDCS sessions (2 mA for 20 min) administered twice daily over 5 consecutive days. Both groups improved significantly over the 5 days of treatment but the bipolar cohort showed greater durability of treatment response at 1 month follow-up with mean reduction in depression scores from baseline being 5% for the unipolar group and 50% for the bipolar group. Similarly, though not formally analysed due to a small sample size, Loo et al. [27] found that 4 of 6 bipolar participants, who completed 3–6 weeks of active tDCS, met the criterion for antidepressant response. In participants, who received 6 weeks of active tDCS, the mean improvement in depression scores was 60% for the bipolar group (N = 4) and 48% for the unipolar group (N = 23). At 1 month follow-up of the same participants, 50% (2 of 4) of bipolar and 39% (9 of 23) of unipolar participants were responders.

If such results were to be confirmed in the current study, tDCS may offer a major development in treating a patient population that suffers higher rates of psychomotor retardation, greater cognitive difficulties, stronger melancholic symptoms (specifically, greater early morning awakening, greater diurnal variation with morning worsening of mood) and higher frequency of psychotic symptoms compared to unipolar depression [31]. Though considered a safe and well tolerated procedure given all current available data, firmer evidence is warranted to assess the risk of inducing manic/hypomanic symptoms with tDCS. Case reports of participants in tDCS studies becoming hypomanic despite being on mood stabiliser medication have been reported [20]. While the hypomanic symptoms resolved within a few days of tDCS cessation, further research is needed as to what extra precautions are needed for bipolar patients and whether any unanticipated safety risks may arise.

In terms of safety considerations, the inclusion of a targeted neuropsychological battery has allowed for evaluation of safety at the higher tDCS 'dose' used in the trial and also enabled investigation of potential cumulative cognitive benefits (e.g., enhanced processing speed) from treatment. No studies to date have reported any major adverse cognitive effects with tDCS. In fact, there is increasing research interest in the potential for cognitive enhancement using tDCS [4,21,53]. Transient cognitive enhancing effects of a single session of tDCS have been shown in multiple studies conducted in healthy participants [13], with similar cognitive enhancing effects on frontal 'executive' functions observed in depressed patients [27,33] and in euthymic patients with bipolar disorder [29]. Cumulative cognitive enhancement effects following repeated treatments in executive functions have also been reported in smaller studies conducted in depressed patients [19] and patients with schizophrenia [52]. However, such findings of improved performance have yet to be replicated in larger controlled trials in depressed samples [11,27].

A secondary but potentially significant issue with regard to any therapeutic application is the determination of individual predictors of response. There is preliminary evidence for a possible influence of brain-derived neurotrophic factor (BDNF) – a nerve growth factor that promotes the growth and survival of neurons – on the effectiveness of tDCS [3,17]. Although the exact mechanisms of action are yet to be completely understood, current evidence suggests that BDNF release associated with the Val66Met polymorphism results in better response to tDCS compared to other brain stimulation techniques such as rTMS, with Val66Met carriers showing motor cortical excitability changes congruent with anodal [3,17] and cathodal tDCS [3]. Moreover, Val66Met carriers tended to show more prolonged excitation responses following anodal tDCS, lasting at least 60 min compared to 20 min for Val homozygotes, and suppression after cathodal tDCS lasting 30 min compared to 20 min for Val homozygotes [3]. However, these studies were conducted with healthy samples and it remains to be seen whether such an effect would translate to clinical response to tDCS.

To our knowledge, this study is one of the most methodologically rigorous tDCS clinical trials and has the potential to provide definitive data on tDCS as an antidepressant treatment. The triple-blinded design with raters, participants and tDCS administrators all blinded to tDCS condition in addition to blinding of the research staff member conducting the primary statistical analysis will minimise the potential for any bias or compromising of data. The sample size will equal that of the largest tDCS trial conducted to date [11] but being an international 6-site multicentre study, will further test the efficacy of tDCS across a broader sampling of participants thereby enhancing generalizability. If found to be effective, results from this study will provide further

impetus to the translation of tDCS into more widespread clinical use for both unipolar and bipolar patients. tDCS offers a cost effective, well tolerated and relatively easy-to-operate non-invasive brain stimulation treatment. Although there are established treatments for depression, the large scale Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial conducted in a real-world setting found one-third of unipolar depressed patients remained depressed even after four trials of antidepressant medications [44,56]. Similarly, in the large scale Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) trial of bipolar depression, treatment with a mood stabiliser led to treatment response in approximately one-third of patients, with one quarter attaining a durable recovery, but without additional benefit from adjunctive antidepressant medication [46]. While electroconvulsive therapy (ECT) stands as the most effective treatment for depression with response rates of approximately 60–70% in depressed patients [22,39,41,47], treatment uptake and adherence are constrained by concerns over cognitive side effects, need for hospital visits, and a specialised treatment unit for general anaesthesia and ECT. Further, seminal studies show relapse rates of 84% after initial improvement with acute ECT treatment although this was reduced to 60% relapse with continuation medication [48] or continuation-ECT [26].

Thus, more treatment options are needed for both unipolar and bipolar depression. Indeed, there is now rapidly growing interest in developing self-operated, home-based tDCS devices that can further facilitate accessibility to tDCS treatment [12]. Such home-based treatment provision is currently infeasible with other brain stimulation treatments (e.g., rTMS). tDCS could therefore prove to be a useful antidepressant neurostimulation addition to the neuropsychiatric armamentarium.

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References

[1] E.G. Altman, D. Hedeker, J.L. Peterson, J.M. Davis, The Altman Self-Rating Mania Scale, Biol. Psychiatry 42 (1997) 948–955.
[2] American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders, 4th ed., 2000 (Text Revision, Washington, DC).
[3] A. Antal, L. Chaieb, V. Moliadze, K. Monte-Silva, C. Poreisz, N. Thirugnanasambandam, M.A. Nitsche, M. Shoukier, H. Ludwig, W. Paulus, Brain-derived neurotrophic factor (BDNF) gene polymorphisms shape cortical plasticity in humans, Brain Stimul. 3 (2010) 230–237.
[4] D. Bennabi, S. Pedron, E. Haffen, J. Monnin, Y. Peterschmitt, V. Van Waes, Transcranial direct current stimulation for memory enhancement: from clinical research to animal models, Front. Syst. Neurosci. 8 (2014) 159.
[5] M. Bikson, D.Q. Truong, A.P. Mourdoukoutas, M. Aboseria, N. Khadka, D. Adair, A. Rahman, Modeling sequence and quasi-uniform assumption in computational neurostimulation, Prog. Brain Res. 222 (2015) 1–23.
[6] L.J. Bindman, O.C. Lippold, J.W. Redfearn, The action of brief polarizing currents on the cerebral cortex of the rat (1) during current flow and (2) in the production of long-lasting after-effects, J. Physiol. 172 (1964) 369–382.
[7] D.E. Broadbent, P.F. Cooper, P. FitzGerald, K.R. Parkes, The Cognitive Failures Questionnaire (CFQ) and its correlates, Br. J. Clin. Psychol. 21 (Pt 1) (1982) 1–16.
[8] A.R. Brunoni, R. Ferrucci, M. Bortolomasi, M. Vergari, L. Tadini, P.S. Boggio, M. Giacopuzzi, S. Barbieri, A. Priori, Transcranial direct current stimulation (tDCS) in unipolar vs. bipolar depressive disorder, Prog. Neuro-Psychopharmacol. Biol. Psychiatry 35 (2011) 96–101.
[9] A.R. Brunoni, A.H. Moffa, F. Fregni, U. Palm, F. Padberg, D.M. Blumberger, Z.J. Daskalakis, D. Bennabi, E. Haffen, A. Alonzo, C.K. Loo, Transcranial direct current stimulation for acute major depressive episodes: meta-analysis of individual patient data, Br. J. Psychiatry (2016).
[10] A.R. Brunoni, B. Sampaio-Junior, A.H. Moffa, L. Borrione, B.S. Nogueira, L.V. Aparicio, B. Veronezi, M. Moreno, R.A. Fernandes, D. Tavares, P.V. Bueno, O. Seibt, M. Bikson, R. Fraguas, I.M. Bensenor, The Escitalopram versus Electric Current Therapy for Treating Depression Clinical Study (ELECT-TDCS): rationale and study design of a non-inferiority, triple-arm, placebo-controlled clinical trial, Sao Paulo Med. J. = Rev. Paul. Med. 133 (2015) 252–263.
[11] A.R. Brunoni, L. Valiengo, A. Baccaro, T.A. Zanao, J.F. de Oliveira, A. Goulart, P.S. Boggio, P.A. Lotufo, I.M. Bensenor, F. Fregni, The sertraline vs. electrical current therapy for treating depression clinical study: results from a factorial, randomized, controlled trial, JAMA Psychiat. 70 (2013) 383–391.
[12] L.E. Charvet, M. Kasschau, A. Datta, H. Knotkova, M.C. Stevens, A. Alonzo, C. Loo, K.R. Krull, M. Bikson, Remotely-supervised transcranial direct current stimulation (tDCS) for clinical trials: guidelines for technology and protocols, Front. Syst. Neurosci. 9 (2015) 26.
[13] B.A. Coffman, V.P. Clark, R. Parasuraman, Battery powered thought: enhancement of attention, learning, and memory in healthy adults using transcranial direct current stimulation, NeuroImage 85 (Pt 3) (2014) 895–908.
[14] A. Datta, D. Truong, P. Minhas, L.C. Parra, M. Bikson, Inter-individual variation during transcranial direct current stimulation and normalization of dose using MRI-derived computational models, Front. Psych. 3 (2012) 91.
[15] D.C. Delis, E. Kaplan, J.H. Kramer, Delis-Kaplan Executive Function System (D-KEFS), The Psychological Corporation, San Antonio, TX, 2001.
[16] D.C. Delis, J.H. Kramer, E. Kaplan, B.A. Ober, California Verbal Learning Test, 2nd ed. The Psychological Corporation, San Antonio, TX, 2000.
[17] V. Di Lazzaro, F. Manganelli, M. Dileone, F. Notturno, M. Esposito, M. Capasso, R. Dubbioso, M. Pace, F. Ranieri, G. Minicuci, L. Santoro, A. Uncini, The effects of prolonged cathodal direct current stimulation on the excitatory and inhibitory circuits of the ipsilateral and contralateral motor cortex, J. Neural Transm. (Vienna) 119 (2012) 1499–1506.
[18] J. Endicott, J. Nee, W. Harrison, R. Blumenthal, Quality of Life Enjoyment and Satisfaction Questionnaire: a new measure, Psychopharmacol. Bull. 29 (1993) 321–326.
[19] F. Fregni, P.S. Boggio, M.A. Nitsche, S.P. Rigonatti, A. Pascual-Leone, Cognitive effects of repeated sessions of transcranial direct current stimulation in patients with depression, Depress. Anxiety 23 (2006) 482–484.
[20] V. Galvez, A. Alonzo, D. Martin, P.B. Mitchell, P. Sachdev, C.K. Loo, Hypomania induction in a patient with bipolar II disorder by transcranial direct current stimulation (tDCS), J. ECT 27 (2011) 256–258.
[21] J. Gill, P.P. Shah-Basak, R. Hamilton, It's the thought that counts: examining the task-dependent effects of transcranial direct current stimulation on executive function, Brain Stimul. 8 (2015) 253–259.
[22] Group, U.E.R, Efficacy and safety of electroconvulsive therapy in depressive disorders: a systematic review and meta-analysis, Lancet 361 (2003) 799–808.
[23] R. Gueorguieva, J.H. Krystal, Move over ANOVA: progress in analyzing repeated-measures data and its reflection in papers published in the Archives of General Psychiatry, Arch. Gen. Psychiatry 61 (2004) 310–317.
[24] C. Hahn, J. Rice, S. Macuff, P. Minhas, A. Rahman, M. Bikson, Methods for extra-low voltage transcranial direct current stimulation: current and time dependent impedance decreases, Clin. Neurophysiol. 124 (2013) 551–556.
[25] U.G. Kalu, C.E. Sexton, C.K. Loo, K.P. Ebmeier, Transcranial direct current stimulation in the treatment of major depression: a meta-analysis, Psychol. Med. 42 (2012) 1791–1800.
[26] C.H. Kellner, R.G. Knapp, G. Petrides, T.A. Rummans, M.M. Husain, K. Rasmussen, M. Mueller, H.J. Bernstein, K. O'Connor, G. Smith, M. Biggs, S.H. Bailine, C. Malur, E. Yim, S. McClintock, S. Sampson, M. Fink, Continuation electroconvulsive therapy vs pharmacotherapy for relapse prevention in major depression: a multisite study from the Consortium for Research in Electroconvulsive Therapy (CORE), Arch. Gen. Psychiatry 63 (2006) 1337–1344.
[27] C.K. Loo, A. Alonzo, D. Martin, P.B. Mitchell, V. Galvez, P. Sachdev, Transcranial direct current stimulation for depression: 3-week, randomised, sham-controlled trial, Br. J. Psychiatry 200 (2012) 52–59.
[28] C.K. Loo, P. Sachdev, D. Martin, M. Pigot, A. Alonzo, G.S. Malhi, J. Lagopoulos, P. Mitchell, A double-blind, sham-controlled trial of transcranial direct current stimulation for the treatment of depression, Int. J. Neuropsychopharmacol. 13 (2010) 61–69.
[29] D.M. Martin, H.N. Chan, A. Alonzo, M.J. Green, P.B. Mitchell, C.K. Loo, Transcranial direct current stimulation to enhance cognition in euthymic bipolar disorder, Bipolar Disord. 17 (2015) 849–858.
[30] D. Meron, N. Hedger, M. Garner, D.S. Baldwin, Transcranial direct current stimulation (tDCS) in the treatment of depression: systematic review and meta-analysis of efficacy and tolerability, Neurosci. Biobehav. Rev. 57 (2015) 46–62.
[31] P.B. Mitchell, G.M. Goodwin, G.F. Johnson, R.M. Hirschfeld, Diagnostic guidelines for bipolar depression: a probabilistic approach, Bipolar Disord. 10 (2008) 144–152.
[32] S.A. Montgomery, M. Asberg, A new depression scale designed to be sensitive to change, Br. J. Psychiatry 134 (1979) 382–389.
[33] M.L. Moreno, M.A. Vanderhasselt, A.F. Carvalho, A.H. Moffa, P.A. Lotufo, I.M. Bensenor, A.R. Brunoni, Effects of acute transcranial direct current stimulation in hot and cold working memory tasks in healthy and depressed subjects, Neurosci. Lett. 591 (2015) 126–131.
[34] C.J.L. Murray, T. Vos, R. Lozano, M. Naghavi, A.D. Flaxman, C. Michaud, M. Ezzati, K. Shibuya, J.A. Salomon, S. Abdalla, V. Aboyans, J. Abraham, I. Ackerman, R. Aggarwal, S.Y. Ahn, M.K. Ali, M. Alvarado, H.R. Anderson, L.M. Anderson, K.G. Andrews, C. Atkinson, L.M. Baddour, A.N. Bahalim, S. Barker-Collo, L.H. Barrero, D.H. Bartels, M.G. Basanez, A. Baxter, M.L. Bell, E.J. Benjamin, D. Bennett, E. Bernabe, K. Bhalla, B. Bhandari, B. Bikbov, A. Bin Abdulhak, G. Birbeck, J.A. Black, H. Blencowe, J.D. Blore, F. Blyth, I. Bolliger, A. Bonaventure, S.A. Boufous, R. Bourne, M. Boussinesq, T. Braithwaite, C. Brayne, L. Bridgett, S. Brooker, P. Brooks, T.S. Brugha, C. Bryan-Hancock, C. Bucello, R. Buchbinder, G. Buckle, C.M. Budke, M. Burch, P. Burney, R. Burstein, B. Calabria, B. Campbell, C.E. Canter, H. Carabin, J. Carapetis, L. Carmona, C. Cella, F. Charlson, H.L. Chen, A.T.A. Cheng, D. Chou, S.S. Chugh, L.E. Coffeng, S.D. Colan, S. Colquhoun, K.E. Colson, J. Condon, M.D. Connor, L.T. Cooper, M. Corriere, M. Cortinovis, K.C. De Vaccaro, W. Couser, B.C. Cowie, M.H. Criqui, M. Cross, K.C. Dabhadkar, M. Dahiya, N. Dahodwala, J. Damsere-Derry, G. Danaei, A. Davis, D. De Leo, L. Degenhardt, R. Dellavalle, A. Delossantos, J. Denenberg, S. Derrett, D.C. Des Jarlais, S.D. Dharmaratne, M. Dherani, C. Diaz-Torne, H. Dolk, E.R. Dorsey, T. Driscoll, H. Duber, B. Ebel, K. Edmond, A. Elbaz, S.E. Ali, H. Erskine, P.J. Erwin, P. Espindola, S.E. Ewoigbokhan, F. Farzadfar, V. Feigin, D.T. Felson, A. Ferrari, C.P. Ferri, E.M. Fevre, M.M. Finucane, S. Flaxman, L. Flood, K. Foreman, M.H. Forouzanfar, F.G.R. Fowkes, M. Fransen, M.K. Freeman, B.J. Gabbe, S.E. Gabriel, E. Gakidou, H.A. Ganatra, B. Garcia, F. Gaspari, R.F. Gillum, G. Gmel, D.

Gonzalez-Medina, R. Gosselin, R. Grainger, B. Grant, J. Groeger, F. Guillemin, D. Gunnell, R. Gupta, J. Haagsma, H. Hagan, Y.A. Halasa, W. Hall, D. Haring, J.M. Haro, J.E. Harrison, R. Havmoeller, R.J. Hay, H. Higashi, C. Hill, B. Hoen, H. Hoffman, P.J. Hotez, D. Hoy, J.J. Huang, S.E. Ibeanusi, K.H. Jacobsen, S.L. James, D. Jarvis, R. Jasrasaria, S. Jayaraman, N. Johns, J.B. Jonas, G. Karthikeyan, N. Kassebaum, N. Kawakami, A. Keren, J.P. Khoo, C.H. King, L.M. Knowlton, O. Kobusingye, A. Koranteng, R. Krishnamurthi, F. Laden, R. Lalloo, L.L. Laslett, T. Lathlean, J.L. Leasher, Y.Y. Lee, J. Leigh, D. Levinson, S.S. Lim, E. Limb, J.K. Lin, M. Lipnick, S.E. Lipshultz, W. Liu, M. Loane, S.L. Ohno, R. Lyons, J. Mabweijano, M.F. MacIntyre, R. Malekzadeh, L. Mallinger, S. Manivannan, W. Marcenes, L. March, D.J. Margolis, G.B. Marks, R. Marks, A. Matsumori, R. Matzopoulos, B.M. Mayosi, J.H. McAnulty, M.M. McDermott, N. McGill, J. McGrath, M.E. Medina-Mora, M. Meltzer, G.A. Mensah, T.R. Merriman, A.C. Meyer, V. Miglioli, M. Miller, T.R. Miller, P.B. Mitchell, C. Mock, A.O. Mocumbi, T.E. Moffitt, A.A. Mokdad, L. Monasta, M. Montico, M. Moradi-Lakeh, A. Moran, L. Morawska, R. Mori, M.E. Murdoch, M.K. Mwaniki, K. Naidoo, M.N. Nair, L. Naldi, K.M.V. Narayan, P.K. Nelson, R.G. Nelson, M.C. Nevitt, C.R. Newton, S. Nolte, P. Norman, R. Norman, M. O'Donnell, S. O'Hanlon, C. Olives, S.B. Omer, K. Ortblad, R. Osborne, D. Ozgediz, A. Page, B. Pahari, J.D. Pandian, A.P. Rivero, S.B. Patten, N. Pearce, R.P. Padilla, F. Perez-Ruiz, N. Perico, K. Pesudovs, D. Phillips, M.R. Phillips, K. Pierce, S. Pion, G.V. Polanczyk, S. Polinder, C.A. Pope, S. Popova, E. Porrini, F. Pourmalek, M. Prince, R.L. Pullan, K.D. Ramaiah, D. Ranganathan, H. Razavi, M. Regan, J.T. Rehm, D.B. Rein, G. Remuzzi, K. Richardson, F.P. Rivara, T. Roberts, C. Robinson, F.R. De Leon, L. Ronfani, R. Room, L.C. Rosenfeld, L. Rushton, R.L. Sacco, S. Saha, U. Sampson, L. Sanchez-Riera, E. Sanman, D.C. Schwebel, J.G. Scott, M. Segui-Gomez, S. Shahraz, D.S. Shepard, H. Shin, R. Shivakoti, D. Singh, G.M. Singh, J.A. Singh, J. Singleton, D.A. Sleet, K. Sliwa, E. Smith, J.L. Smith, N.J.C. Stapelberg, A. Steer, T. Steiner, W.A. Stolk, L.J. Stovner, C. Sudfeld, S. Syed, G. Tamburlini, M. Tavakkoli, H.R. Taylor, J.A. Taylor, W.J. Taylor, B. Thomas, W.M. Thomson, G.D. Thurston, I.M. Tleyjeh, M. Tonelli, J.R.A. Towbin, T. Truelsen, M.K. Tsilimbaris, C. Ubeda, E.A. Undurraga, M.J. van der Werf, J. van Os, M.S. Vavilala, N. Venketasubramanian, M.R. Wang, W.Z. Wang, K. Watt, D.J. Weatherall, M.A. Weinstock, R. Weintraub, M.G. Weisskopf, M.M. Weissman, R.A. White, H. Whiteford, N. Wiebe, S.T. Wiersma, J.D. Wilkinson, H.C. Williams, S.R.M. Williams, E. Witt, F. Wolfe, A.D. Woolf, S. Wulf, P.H. Yeh, A.K.M. Zaidi, Z.J. Zheng, D. Zonies, A.D. Lopez, Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010, Lancet 380 (2012) 2197–2223.

[35] Z.S. Nasreddine, N.A. Phillips, V. Bedirian, S. Charbonneau, V. Whitehead, I. Collin, J.L. Cummings, H. Chertkow, The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment, J. Am. Geriatr. Soc. 53 (2005) 695–699.

[36] M.A. Nitsche, W. Paulus, Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation, J. Physiol. 527 (Pt 3) (2000) 633–639.

[37] U. Palm, C. Schiller, Z. Fintescu, M. Obermeier, D. Keeser, E. Reisinger, O. Pogarell, M.A. Nitsche, H.J. Moller, F. Padberg, Transcranial direct current stimulation in treatment resistant depression: a randomized double-blind, placebo-controlled study, Brain Stimul. 5 (2012) 242–251.

[38] S. Pereira Junior Bde, G. Tortella, B. Lafer, P. Nunes, I.M. Bensenor, P.A. Lotufo, R. Machado-Vieira, A.R. Brunoni, The bipolar depression electrical treatment trial (BETTER): design, rationale, and objectives of a randomized, sham-controlled trial and data from the pilot study phase, Neural Plast. 2015 (2015) 684025.

[39] G. Petrides, M. Fink, M.M. Husain, R.G. Knapp, A.J. Rush, M. Mueller, T.A. Rummans, K.M. O'Connor, K.G. Rasmussen Jr., H.J. Bernstein, M. Biggs, S.H. Bailine, C.H. Kellner, ECT remission rates in psychotic versus nonpsychotic depressed patients: a report from CORE, J. ECT 17 (2001) 244–253.

[40] C. Poreisz, K. Boros, A. Antal, W. Paulus, Safety aspects of transcranial direct current stimulation concerning healthy subjects and patients, Brain Res. Bull. 72 (2007) 208–214.

[41] J. Prudic, M. Olfson, S.C. Marcus, R.B. Fuller, H.A. Sackeim, Effectiveness of electroconvulsive therapy in community settings, Biol. Psychiatry 55 (2004) 301–312.

[42] L.L. Richmond, D.A. Wolk, H.B. Coslett, G. Vyas, I.R. Olson, Repeated daily exposure to direct current stimulation does not result in sustained or notable side effects, Brain Stimul. 6 (2013) 974–976.

[43] R.M. Ruff, C.C. Allen, Ruff 2 and 7 Selective Attention Test Professional Manual, Psychological Assessment Resources, Inc., Odessa, FL, 1996.

[44] A.J. Rush, Limitations in efficacy of antidepressant monotherapy, J. Clin. Psychiatry 68 (Suppl. 10) (2007) 8–10.

[45] A.J. Rush, M.H. Trivedi, H.M. Ibrahim, T.J. Carmody, B. Arnow, D.N. Klein, J.C. Markowitz, P.T. Ninan, S. Kornstein, R. Manber, M.E. Thase, J.H. Kocsis, M.B. Keller, The 16-item Quick Inventory of Depressive Symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression, Biol. Psychiatry 54 (2003) 573–583.

[46] G.S. Sachs, A.A. Nierenberg, J.R. Calabrese, L.B. Marangell, S.R. Wisniewski, L. Gyulai, E.S. Friedman, C.L. Bowden, M.D. Fossey, M.J. Ostacher, T.A. Ketter, J. Patel, P. Hauser, D. Rapport, J.M. Martinez, M.H. Allen, D.J. Miklowitz, M.W. Otto, E.B. Dennehy, M.E. Thase, Effectiveness of adjunctive antidepressant treatment for bipolar depression, N. Engl. J. Med. 356 (2007) 1711–1722.

[47] H.A. Sackeim, E.M. Dillingham, J. Prudic, T. Cooper, W.V. McCall, P. Rosenquist, K. Isenberg, K. Garcia, B.H. Mulsant, R.F. Haskett, Effect of concomitant pharmacotherapy on electroconvulsive therapy outcomes: short-term efficacy and adverse effects, Arch. Gen. Psychiatry 66 (2009) 729–737.

[48] H.A. Sackeim, R.F. Haskett, B.H. Mulsant, M.E. Thase, J.J. Mann, H.M. Pettinati, R.M. Greenberg, R.R. Crowe, T.B. Cooper, J. Prudic, Continuation pharmacotherapy in the prevention of relapse following electroconvulsive therapy: a randomized controlled trial, JAMA 285 (2001) 1299–1307.

[49] D.V. Sheehan, Y. Lecrubier, K.H. Sheehan, P. Amorim, J. Janavs, E. Weiller, T. Hergueta, R. Baker, G.C. Dunbar, The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10, J. Clin. Psychiatry 59 (Suppl. 20) (1998) 22–33 (quiz 34-57).

[50] P. Shiozawa, F. Fregni, I.M. Bensenor, P.A. Lotufo, M.T. Berlim, J.Z. Daskalakis, Q. Cordeiro, A.R. Brunoni, Transcranial direct current stimulation for major depression: an updated systematic review and meta-analysis, Int. J. Neuropsychopharmacol. 17 (2014) 1443–1452.

[51] A. Smith, Symbol Digit Modalities Test, Western Psychological Services, Los Angeles, CA, 1991.

[52] R.C. Smith, S. Boules, S. Mattiuz, M. Youssef, R.H. Tobe, H. Sershen, A. Lajtha, K. Nolan, R. Amiaz, J.M. Davis, Effects of transcranial direct current stimulation (tDCS) on cognition, symptoms, and smoking in schizophrenia: a randomized controlled study, Schizophr. Res. 168 (2015) 260–266.

[53] R. Sparing, M. Dafotakis, I.G. Meister, N. Thirugnanasambandam, G.R. Fink, Enhancing language performance with non-invasive brain stimulation–a transcranial direct current stimulation study in healthy humans, Neuropsychologia 46 (2008) 261–268.

[54] D.Q. Truong, G. Magerowski, G.L. Blackburn, M. Bikson, M. Alonso-Alonso, Computational modeling of transcranial direct current stimulation (tDCS) in obesity: impact of head fat and dose guidelines, NeuroImage Clin. 2 (2013) 759–766.

[55] T. Vos, A.D. Flaxman, M. Naghavi, R. Lozano, C. Michaud, M. Ezzati, K. Shibuya, J.A. Salomon, S. Abdalla, V. Aboyans, J. Abraham, I. Ackerman, R. Aggarwal, S.Y. Ahn, M.K. Ali, M. Alvarado, H.R. Anderson, L.M. Anderson, K.G. Andrews, C. Atkinson, L.M. Baddour, A.N. Bahalim, S. Barker-Collo, L.H. Barrero, D.H. Bartels, M.G. Basanez, A. Baxter, M.L. Bell, E.J. Benjamin, D. Bennett, E. Bernabe, K. Bhalla, B. Bhandari, B. Bikbov, A. Bin Abdulhak, G. Birbeck, J.A. Black, H. Blencowe, J.D. Blore, F. Blyth, I. Bolliger, A. Bonaventure, S.A. Boufous, R. Bourne, M. Boussinesq, T. Braithwaite, C. Brayne, L. Bridgett, S. Brooker, P. Brooks, T.S. Brugha, C. Bryan-Hancock, C. Bucello, R. Buchbinder, G.R. Buckle, C.M. Budke, M. Burch, P. Burney, R. Burstein, B. Calabria, B. Campbell, C.E. Canter, H. Carabin, J. Carapetis, L. Carmona, C. Cella, F. Charlson, H.L. Chen, A.T.A. Cheng, D. Chou, S.S. Chugh, L.E. Coffeng, S.D. Colan, S. Colquhoun, K.E. Colson, J. Condon, M.D. Connor, L.T. Cooper, M. Corriere, M. Cortinovis, K.C. de Vaccaro, W. Couser, B.C. Cowie, M.H. Criqui, M. Cross, K.C. Dabhadkar, M. Dahiya, N. Dahodwala, J. Damsere-Derry, G. Danaei, A. Davis, D. De Leo, L. Degenhardt, R. Dellavalle, A. Delossantos, J. Denenberg, S. Derrett, D.C. Des Jarlais, S.D. Dharmaratne, M. Dherani, C. Diaz-Torne, H. Dolk, E.R. Dorsey, T. Driscoll, H. Duber, B. Ebel, K. Edmond, A. Elbaz, S.E. Ali, H. Erskine, P.J. Erwin, P. Espindola, S.E. Ewoigbokhan, F. Farzadfar, V. Feigin, D.T. Felson, A. Ferrari, C.P. Ferri, E.M. Fevre, M.M. Finucane, S. Flaxman, L. Flood, K. Foreman, M.H. Forouzanfar, F.G.R. Fowkes, R. Franklin, M. Fransen, M.K. Freeman, B.J. Gabbe, S.E. Gabriel, E. Gakidou, H.A. Ganatra, B. Garcia, F. Gaspari, R.F. Gillum, G. Gmel, R. Gosselin, R. Grainger, J. Groeger, F. Guillemin, D. Gunnell, R. Gupta, J. Haagsma, H. Hagan, Y.A. Halasa, W. Hall, D. Haring, J.M. Haro, J.E. Harrison, R. Havmoeller, R.J. Hay, H. Higashi, C. Hill, B. Hoen, H. Hoffman, P.J. Hotez, D. Hoy, J.J. Huang, S.E. Ibeanusi, K.H. Jacobsen, S.L. James, D. Jarvis, R. Jasrasaria, S. Jayaraman, N. Johns, J.B. Jonas, G. Karthikeyan, N. Kassebaum, N. Kawakami, A. Keren, J.P. Khoo, C.H. King, L.M. Knowlton, O. Kobusingye, A. Koranteng, R. Krishnamurthi, R. Lalloo, L.L. Laslett, T. Lathlean, J.L. Leasher, Y.Y. Lee, J. Leigh, S.S. Lim, E. Limb, J.K. Lin, M. Lipnick, S.E. Lipshultz, W. Liu, M. Loane, S.L. Ohno, R. Lyons, J.X. Ma, J. Mabweijano, M.F. MacIntyre, R. Malekzadeh, L. Mallinger, S. Manivannan, W. Marcenes, L. March, D.J. Margolis, G.B. Marks, R. Marks, A. Matsumori, R. Matzopoulos, B.M. Mayosi, J.H. McAnulty, M.M. McDermott, N. McGill, J. McGrath, M.E. Medina-Mora, M. Meltzer, G.A. Mensah, T.R. Merriman, A.C. Meyer, V. Miglioli, M. Miller, T.R. Miller, P.B. Mitchell, A.O. Mocumbi, T.E. Moffitt, A.A. Mokdad, L. Monasta, M. Montico, M. Moradi-Lakeh, A. Moran, L. Morawska, R. Mori, M.E. Murdoch, M.K. Mwaniki, K. Naidoo, M.N. Nair, L. Naldi, K.M.V. Narayan, P.K. Nelson, R.G. Nelson, M.C. Nevitt, C.R. Newton, S. Nolte, P. Norman, R. Norman, M. O'Donnell, S. O'Hanlon, C. Olives, S.B. Omer, K. Ortblad, R. Osborne, D. Ozgediz, A. Page, B. Pahari, J.D. Pandian, A.P. Rivero, S.B. Patten, N. Pearce, R.P. Padilla, F. Perez-Ruiz, N. Perico, K. Pesudovs, D. Phillips, M.R. Phillips, K. Pierce, S. Pion, G.V. Polanczyk, S. Polinder, C.A. Pope, S. Popova, E. Porrini, F. Pourmalek, M. Prince, R.L. Pullan, K.D. Ramaiah, D. Ranganathan, H. Razavi, M. Regan, J.T. Rehm, D.B. Rein, G. Remuzzi, K. Richardson, F.P. Rivara, T. Roberts, C. Robinson, F.R. De Leon, L. Ronfani, R. Room, L.C. Rosenfeld, L. Rushton, R.L. Sacco, S. Saha, U. Sampson, L. Sanchez-Riera, E. Sanman, D.C. Schwebel, J.G. Scott, M. Segui-Gomez, S. Shahraz, D.S. Shepard, H. Shin, R. Shivakoti, D. Singh, G.M. Singh, J.A. Singh, J. Singleton, D.A. Sleet, K. Sliwa, E. Smith, J.L. Smith, N.J.C. Stapelberg, A. Steer, T. Steiner, W.A. Stolk, L.J. Stovner, C. Sudfeld, S. Syed, G. Tamburlini, M. Tavakkoli, H.R. Taylor, J.A. Taylor, W.J. Taylor, B. Thomas, W.M. Thomson, G.D. Thurston, I.M. Tleyjeh, M. Tonelli, J.R.A. Towbin, T. Truelsen, M.K. Tsilimbaris, C. Ubeda, E.A. Undurraga, M.J. van der Werf, J. van Os, M.S. Vavilala, N. Venketasubramanian, M.R. Wang, W.Z. Wang, K. Watt, D.J. Weatherall, M.A. Weinstock, R. Weintraub, M.G. Weisskopf, M.M. Weissman, R.A. White, H. Whiteford, S.T. Wiersma, J.D. Wilkinson, H.C. Williams, S.R.M. Williams, E. Witt, F. Wolfe, A.D. Woolf, S. Wulf, P.H. Yeh, A.K.M. Zaidi, Z.J. Zheng, D. Zonies, A.D. Lopez, C.J.L. Murray, Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010, Lancet 380 (2012) 2163–2196.

[56] D. Warden, A.J. Rush, M.H. Trivedi, M. Fava, S.R. Wisniewski, The STAR*D project results: a comprehensive review of findings, Curr. Psychiatry Rep. 9 (2007) 449–459.

[57] D. Wechsler, Wechsler Test of Adult Reading, The Psychological Corporation, New York, 2001.

[58] D. Wechsler, Wechsler Adult Intelligence Scale, 4th ed. Pearson, San Antonio, TX, 2008.

[59] R.C. Young, J.T. Biggs, V.E. Ziegler, D.A. Meyer, A rating scale for mania: reliability, validity and sensitivity, Br. J. Psychiatry 133 (1978) 429–435.