



## International randomized-controlled trial of transcranial Direct Current Stimulation in depression



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### ABSTRACT

**Background:** Evidence suggests that transcranial Direct Current Stimulation (tDCS) has antidepressant effects in unipolar depression, but there is limited information for patients with bipolar depression. Additionally, prior research suggests that brain derived neurotrophic factor (BDNF) Val66Met genotype may moderate response to tDCS.

**Objective:** To examine tDCS efficacy in unipolar and bipolar depression and assess if BDNF genotype is associated with antidepressant response to tDCS.

**Methods:** 130 participants diagnosed with a major depressive episode were randomized to receive active (2.5 milliamps (mA), 30 min) or sham (0.034 mA and two 60-second current ramps up to 1 and 0.5 mA) tDCS to the left prefrontal cortex, administered in 20 sessions over 4 weeks, in a double-blinded, international multisite study. Mixed effects repeated measures analyses assessed change in mood and neuropsychological scores in participants with at least one post-baseline rating in the unipolar ( $N = 84$ ) and bipolar ( $N = 36$ ) samples.

**Results:** Mood improved significantly over the 4-week treatment period in both unipolar ( $p = 0.001$ ) and bipolar groups ( $p < 0.001$ ). Among participants with unipolar depression, there were more remitters in the sham treatment group ( $p = 0.03$ ). There was no difference between active and sham stimulation in the bipolar sample. BDNF genotype was unrelated to antidepressant outcome.

**Conclusions:** Overall, this study found no antidepressant difference between active and sham stimulation for unipolar or bipolar depression. However, the possibility that the low current delivered in the sham tDCS condition was biologically active cannot be discounted. Moreover, BDNF genotype did not moderate antidepressant outcome.

**Clinical Trials Registration:** [www.clinicaltrials.gov](http://www.clinicaltrials.gov), NCT01562184.

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### Introduction

Transcranial Direct Current Stimulation (tDCS) shows promise for the treatment of major depressive disorder (MDD), given reports of efficacy [1], excellent safety [2], and the potential for

translation into home-based, remotely supervised treatment [3]. A recent meta-analysis [1] of randomized controlled trials (RCTs), including the largest double-blind trials at the time [4,5], found tDCS had significantly greater antidepressant effects relative to sham stimulation. As the effect size was small to moderate [1] and most large-scale studies involved only single-centers, further large-scale, multicenter, randomized controlled clinical trials are warranted for confirmation.

Other individual factors have been demonstrated to influence response to tDCS including bipolarity [1] and genetic factors such as the single nucleotide polymorphism (SNP) variation in the common coding exon of brain derived neurotrophic factor (BDNF) that causes an amino acid substitution (Val66Met) in proBDNF [6,7]. When taken into account, these factors may explain the antidepressant effect size variability between studies. For example, open label clinical trials to date have suggested that tDCS may be effective in both unipolar and bipolar depression [8], and a recent meta-analysis of tDCS in depression found bipolarity to be a significant positive predictor of treatment outcome [1]. Further, the BDNF (Val66Met) polymorphism may affect individual response to tDCS [7]. The human (Val66Met) BDNF protein differs in intracellular trafficking with the BDNF Val isoform being released more readily by neuronal depolarisation [9]. Positive anodal tDCS is believed to work via increasing neuronal excitability that leads to greater glutamate release and inducible BDNF release [10–12]. Thus, individuals with the BDNF Val/Val genotype may show greater benefit from tDCS. Since BDNF potentiates postsynaptic effects of glutamate leading to synaptic strengthening, more functional BDNF (Val) would be expected to enhance tDCS associated antidepressant effects. The extent to which clinical features and/or BDNF genotype may contribute to the variability in response to tDCS could lead to better predictions of treatment outcome.

This study was designed to assess the efficacy of tDCS in unipolar and bipolar depression in an international, multi-center, randomized controlled clinical trial (International Consortium of Research in tDCS). The study hypothesis was that active tDCS would be more effective than sham tDCS for both unipolar and bipolar depression, reflected in greater improvement in mood scores over the sham-controlled trial period. The study also included an exploratory assessment of BDNF genotype to investigate its impact on antidepressant response to tDCS.

## Materials and methods

**Trial design:** Full details of the study design, rationale, and methods, reported in compliance with CONSORT guidelines have been previously published [13]. The CONSORT checklist is shown in [Supplementary Table 1](#). In brief, this study used a two-arm, parallel, randomized, sham-controlled design with participants allocated to an active or sham tDCS condition on a 1:1 ratio in an initial 4-week RCT phase. Participants, who did not meet remission at the end of the RCT phase, were eligible to subsequently enter a 4-week open label phase. tDCS was administered on consecutive weekdays for 5 days during both the RCT and open label phases. Participants who completed at least 4 weeks of the trial (i.e., completed the RCT alone or the RCT followed by the open label phase) or were in remission, were also eligible to enter a taper phase that consisted of 4 tDCS sessions given weekly. All participants were contacted for a follow-up 1 month from the end of the acute, daily treatment phase, and again at 3 months if they had not relapsed at the 1-month follow up.

Participants were randomly assigned by a computer-generated random number sequence to active or sham tDCS with permuted-block randomization. Randomization was stratified according to whether participants were diagnosed with unipolar or

bipolar depression. All participants, tDCS treaters, and study raters were blinded to the participants' tDCS group allocation in the RCT phase. The blinding was maintained until the entire study was completed, data cleaning was completed, and the database was locked.

The original, planned study sample of 120 participants with at least one post baseline rating included unipolar and bipolar participants in a 1:1 ratio, and was powered to show a difference between active and sham tDCS in unipolar and bipolar groups, based on an effect size of 0.74 derived from a meta-analysis of all available RCTs at the time of study design implementation [14]. However, due to slow recruitment of bipolar participants, the sample size was adjusted such that recruitment of unipolar participants was permitted to continue after the sample of 60 had been reached while recruitment of bipolar participants remained ongoing throughout the study.

**Participants:** At study entry, participants were at least 18 years old; in a current major depressive episode of a minimum 4-week duration, defined according to Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision (DSM-IV-TR) criteria [15] and established using the Mini International Neuropsychiatric Interview (MINI; Version 5.0.0) [16]; and had a total score of at least 20 on the Montgomery-Asberg Depression Rating Scale (MADRS) [17]. 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. Up to 2 mg lorazepam daily, but no long-acting benzodiazepines were permitted. All participants diagnosed with bipolar disorder were required to be on mood stabilizer medication for the duration of the study.

Exclusion criteria included: a current major depressive episode over 3 years duration; failure of more than 3 adequate antidepressant trials in the current episode; DSM-IV-TR diagnosed psychotic disorder; drug or alcohol abuse or dependence in the preceding 3 months before study entry; inadequate response to electroconvulsive therapy (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) at proposed tDCS electrode sites; and pregnancy. Participants were recruited from 6 study sites across Australia (University of New South Wales/Black Dog Institute, UNSW) and the United States of America (Duke University School of Medicine, Emory University, Rowan University, Sheppard Pratt Health System, University of Texas Southwestern Medical Center at Dallas, UTSW).

Participants provided written informed consent for this study that was approved by the institutional review boards at each study site.

**Interventions:** Active tDCS was administered for 30 min per session at 2.5 milliamperes (mA), using  $7 \times 5$  cm electrodes. The anode was centered over the left dorsolateral prefrontal cortex at F3 (10/20 electroencephalogram system) and the cathode over the lateral right frontal area at F8. For sham stimulation, to optimize blinding, 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 minimizing potential neuromodulatory effects. A second ramp up and down to 0.5 mA over 1 min was delivered at either 10 min or 20 min, again to aid blinding. This strategy elicited weak scalp sensations during the session that are thought to be unlikely to produce lasting changes in cortical excitability [18]. The tDCS device also emitted a constant current of 0.034 mA throughout sham stimulation.

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