

A double-blind, sham-controlled trial of transcranial direct current stimulation for the treatment of depression

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Abstract

Two recent sham-controlled studies found that transcranial direct current stimulation (tDCS) was an effective treatment for depression. As tDCS is painless, relatively safe and inexpensive, its efficacy in treating depression warrants further investigation. This double-blind, randomized study tested tDCS at the same stimulation parameters as a previous positive study (1 mA current strength, five treatment sessions, active or sham, given on alternate days) in 40 depressed participants. Anodal stimulation was centred over the left dorsolateral prefrontal cortex, with the cathode placed on the lateral aspect of the contralateral orbit. tDCS was continued up to a total of ten active sessions per participant. Mood outcomes were measured by psychiatrist raters blind to treatment condition using the Montgomery–Åsberg and other depression rating scales. Psychomotor speed was assessed immediately before and after a single tDCS session and attention, frontal executive function, working memory and verbal learning were assessed after each group of five sessions. Overall depression scores improved significantly over ten tDCS treatments, but there was no between-group difference in the five-session, sham-controlled phase. tDCS was found to be safe, with no adverse effects on neuropsychological function, and only minor side-effects. It is recommended that the efficacy of tDCS in depression be further evaluated over a longer treatment period, using enhanced stimulation parameters.

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Introduction

Transcranial direct current stimulation (tDCS) is a non-invasive form of brain stimulation in which a weak direct current is passed through the scalp into underlying cerebral tissue, with a resultant change in cortical excitability (Arul-Anandam & Loo, 2009a). tDCS has been applied in animal models and humans for many decades (Beveridge & Renvoize, 1988). Weak direct current stimulation shifts the resting membrane potential, as shown in animal experiments – anodal

stimulation has been shown to depolarize the soma of pyramidal cells whereas cathodal stimulation hyperpolarizes them (Bindman *et al.* 1964), and these changes outlast the duration of stimulation by minutes to hours. Recent studies using transcranial magnetic stimulation (TMS) to test cortical excitability before and after a period of tDCS stimulation have shown that similar changes occur in the human motor cortex with tDCS (Nitsche & Paulus, 2000).

For decades, there has been the suggestion that tDCS may have antidepressant effects. Beneficial effects of tDCS in depression were reported in the 1960s and 1970s (Arfai *et al.* 1970; Costain *et al.* 1964; Hordern & Weeks, 1965; Lippold & Redfearn, 1964; Lolas, 1977) but were not followed up by investigators. Outcomes in these studies were quite variable,

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probably reflecting the considerable diversity of tDCS methodology used, in terms of electrode placement (various parts of the head, trunk, limbs, etc.), electrode size, current amplitude (20–500 μ A) and stimulation duration (2 min–8 h).

Recently, two double-blind, sham-controlled studies using left prefrontal anodal tDCS at higher stimulation intensities (1–2 mA) reported positive results in reducing depressive symptoms (Boggio *et al.* 2008; Fregni *et al.* 2006a). In the first study (Fregni *et al.* 2006a), a 60% improvement in mean Hamilton Depression Rating Scale (HAMD) scores was reported after only five sessions of active tDCS (20 min at 1 mA), given on alternate weekdays, compared to 10% improvement in the sham group. The second study (from the same group of investigators) similarly reported robust results, with mean improvement in the active group on HAMD scores of 40.5%, compared to 10.4% in the sham group, after 2 wk (ten consecutive weekdays) of treatment (20 min at 2 mA) (Boggio *et al.* 2008). The difference in outcomes between active and sham treatment groups was still evident at 1-month follow-up in the latter study. When these results were compared with those of depressed patients treated with 20 mg fluoxetine (open label), the authors reported that the response to tDCS was of a similar magnitude but of more rapid onset (Rigonatti *et al.* 2008). Regarding safety, tDCS was well tolerated with minimal side-effects (transient headache, skin itching and redness).

These positive results suggest considerable potential for tDCS as an antidepressant treatment, which needs further testing and corroboration in clinical trials. We report the results of a double-blind, sham-controlled trial to test the antidepressant effects of left prefrontal anodal tDCS in depressed subjects.

Methods

Subjects

Forty subjects with unipolar DSM-IV major depressive episode of up to 3 yr duration and a score ≥ 20 on the Montgomery–Asberg Depression Rating Scale (MADRS; Montgomery & Asberg, 1979) were enrolled as outpatients. The diagnosis was based on a structured assessment using the MINI (MINI International Neuropsychiatric Interview; Sheehan *et al.* 1997) and confirmed in a clinical interview by a study psychiatrist (C.K.L.). Subjects with bipolar disorder, drug or alcohol dependence or abuse, other Axis I disorders, neurological disorders, or who had failed to respond to electroconvulsive therapy in the current episode of depression, were excluded.

During the study, subjects were either medication-free or remained on antidepressant medications to which they had failed to respond, continued at stable doses which had not been altered for at least 4 wk prior to enrolment. Six subjects were also on anti-psychotic medications, five subjects were on lithium and one subject was on an anticonvulsant medication (lamotrigine). No subjects were on benzodiazepines. After the study period, patients reverted to routine clinical management under their own treating psychiatrist.

The study was approved by the human research ethics committee of the University of New South Wales. After complete description of the study to the subjects, written informed consent was obtained.

Study design

Subjects were stratified by age and gender and then randomly assigned to active or sham treatment groups. Active or sham tDCS was given three times per week (Monday, Wednesday, Friday), for five treatment sessions with raters and subjects blind to treatment group assignment. All subjects then continued with active tDCS (at the same treatment frequency) for another five sessions. At enrolment, subjects were told that some of the ten treatment sessions may involve sham treatment. Thus subjects were not aware that treatment sessions 6–10 definitely involved active treatment. After the ten sessions, the integrity of the blinding was assessed by asking subjects to guess whether they had been assigned to the active or sham treatment group. Following this, the blind was broken and subjects who had only received five active treatments were given the option of receiving another five active treatments (see Fig. 1).

tDCS treatment

Anodal tDCS was administered over the left dorso-lateral prefrontal cortex (DLPFC), identified as pF3 on the 10/20 EEG system. The first nine subjects were treated using a DC stimulator made by J. Lagopoulos. For subsequent subjects, an Eldith DC-stimulator (NeuroConn GmbH, Germany) was used. The current output of these devices was checked using an ammeter. The cathode was placed over the lateral aspect of the contralateral orbit. Conductive rubber electrodes (7×5 cm = 35 cm²) covered by sponges soaked in saline were used, held in place by a head band. Stimulation was given at 1 mA for 20 min, with gradual ramping up of the current over 30 s. For sham stimulation, the procedure was identical, except that the current was gradually ramped down to zero, after

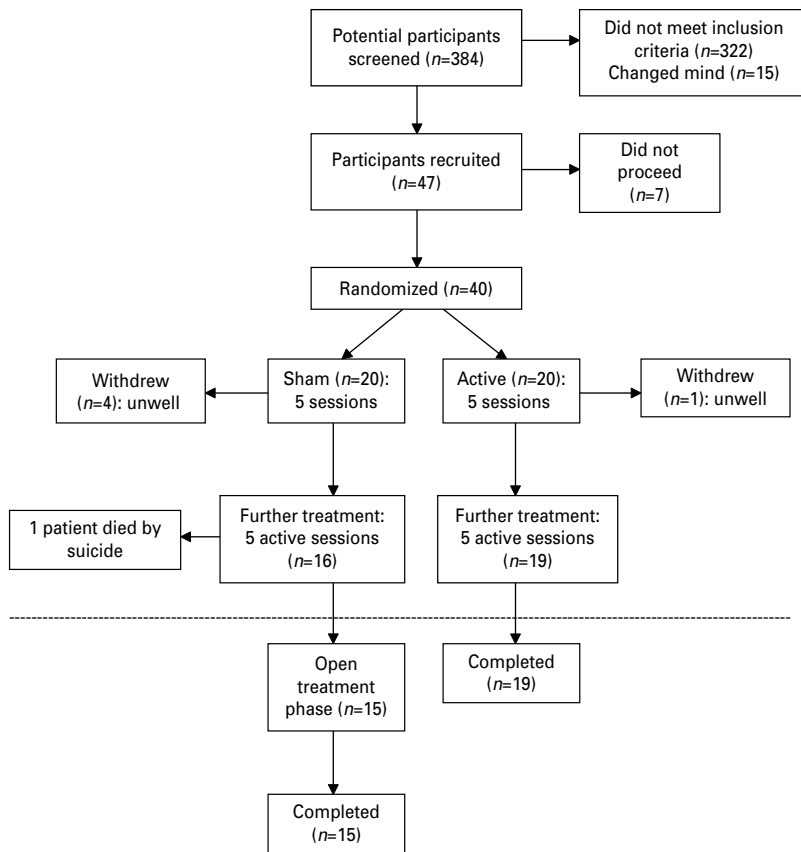


Fig. 1. Diagram showing study design and progress of subjects through the trial. The dotted line indicates breaking of the blind for subjects after which five DCS sessions were offered on an open basis to participants in the sham group.

the first 30 s, thus giving the same initial sensation of tDCS. The switching on and off of the current was programmed into the stimulator and did not require intervention by the operator. The machine was placed behind the subjects' heads so that they were unable to see the readout on the front panel of the stimulator.

Assessment of mood and cognition

The primary outcome measure for mood evaluation was the MADRS. Subjects were evaluated at baseline, after each five treatment sessions, 1 week and 1 month after completion of treatment. All ratings were conducted by a psychiatrist who was blinded to treatment condition, using the MADRS, 17-item HAMD (HAMD₁₇; Hamilton, 1960) and Clinical Global Impression scale – Severity of Illness (CGI-S; Guy, 1976). Each subject was rated by the same psychiatrist throughout the study. At the same time-points, subjects rated their mood using the Beck Depression Inventory (BDI; Beck *et al.* 1961) and Patient Global Impression scale – Improvement of Illness (PGI-I; Guy, 1976). Subjects were also assessed using the Core

Measure of Psychomotor Disturbance (CORE; Parker *et al.* 1990) at baseline, as a possible predictor of response.

Neuropsychological functioning was assessed at baseline and after each five treatment sessions using the following tests: Rey Auditory Verbal Learning Test (RAVLT; Rey, 1964), Trail Making Tests (TMT) A and B (Reitan & Wolfson, 1985), Wechsler Adult Intelligence Scale (WAIS) digit span (forwards and backwards; Wechsler, 1981), Controlled Oral Word Association Test (COWAT; Benton & Hamsher, 1989). Alternative test forms were used on subsequent occasions for RAVLT and COWAT. Immediate effects of tDCS on processing speed were also assessed after treatment sessions 1 and 5 using the Symbol Digit Modalities Test (SDMT; Smith, 1991), and simple and choice reaction-time tests.

Data analysis

The two treatment groups were analysed for differences in demographic and clinical variables at baseline using χ^2 tests for categorical variables and *t* tests for

Table 1. Comparison of demographic and clinical variables at study entry for sham and active groups

	Group, means (s.d.)		d.f.	F/χ^2	p
	Sham	Active			
Age (yr)	45.60 (12.45)	48.95 (10.00)	1, 38	1.10	0.30
Gender (male/female)	9/11 ^a	9/11 ^a	1	0	0.62
Age at onset (yr)	31.85 (14.69)	31.20 (14.05)	1, 38	0.01	0.91
Melancholic/non-melancholic	8/12 ^a	9/11 ^a	1	0.10	0.50
Duration of current episode (months)	21.55 (19.78)	15.85 (12.25)	1, 38	2.64	0.11
Duration of all past episodes (months)	59.60 (103.93)	48.60 (51.18)	1, 38	1.57	0.22
Antidepressants failed current episode	1.70 (1.75)	1.00 (1.49)	1, 38	1.21	0.28
Total lifetime failed antidepressants	3.25 (2.85)	3.15 (2.94)	1, 38	0.05	0.83
Concurrent antidepressant medication (yes/no)	13/7 ^a	7/13 ^a	1	3.60	0.06
Baseline HAMD ₁₇ score	17.25 (4.70)	18.30 (5.75)	1, 38	0.04	0.84
Baseline MADRS score	28.40 (4.44)	29.20 (4.87)	1, 38	0.34	0.56
Baseline CGI score	4.40 (0.68)	4.26 (0.65)	1, 37	0.53	0.47
Baseline CORE total	6.47 (4.81)	4.31 (3.84)	1, 29	0.24	0.63
Baseline BDI score	27.47 (9.93)	27.80 (8.02)	1, 37	1.99	0.17
Baseline PGI score	4.00 (0.00)	4.05 (0.22)	1, 38	4.46	0.04

HAMD₁₇, 17-item Hamilton Depression Rating Scale; MADRS, Montgomery–Asberg Depression Rating Scale; CGI, Clinician Global Impressions; CORE, CORE Measure of Psychomotor Disturbance; BDI, Beck Depression Inventory; PGI, Patient Global Impressions.

^a Actual tally recorded.

dimensional variables (see Table 1). Statistical tests were two-tailed. Intention-to-treat last-observation-carried-forward scores were used for the analyses below.

Depression ratings over the first five treatment sessions were analysed for change with a repeated-measures design (ANOVA), testing for main effects of time and group as well as time \times group interactions. A further repeated-measures analysis of covariance (ANCOVA) was performed on the same data, controlling for concurrent antidepressant treatment. Baseline CORE ratings were correlated (Pearson's correlation) with the percentage change in MADRS scores over the ten active treatment sessions (data pooled across both groups), to see if CORE scores predicted response.

Scores from neuropsychological tests examining for changes over the first five treatment sessions (active or sham), and scores from tests administered immediately before and after a single session of tDCS (active or sham) were also analysed with a repeated-measures design, testing for main effects of time and group as well as time \times group interactions. Neuropsychological test scores were separately analysed for all subjects who received ten active treatments (either in the sham-controlled phase or open treatment phase), examining for changes across the ten sessions, using a repeated-measures ANCOVA, controlling for the percentage

change in MADRS scores over the same treatment period.

To test the integrity of blinding, subjects' responses (active, sham) when asked to guess their treatment group were compared for active and sham groups using a χ^2 test.

Results

Subjects

There were no significant differences between active and sham treatment groups at baseline, although there was a trend for a higher proportion of subjects to be on concurrent antidepressant medication in the sham treatment group (see Table 1). Thirty-five subjects completed the five-session sham-controlled phase and 34 subjects received ten active sessions of tDCS (over both sham-controlled and open treatment phases) (see Fig. 1).

Mood outcomes

There were significant main effects of time over the first five treatment sessions (sham-controlled phase) on the HAMD₁₇ and MADRS, but there were no significant interactions between time and group (see Table 2, Fig. 2). Repeated-measures ANCOVAs on HAMD and MADRS scores, co-varying for concurrent

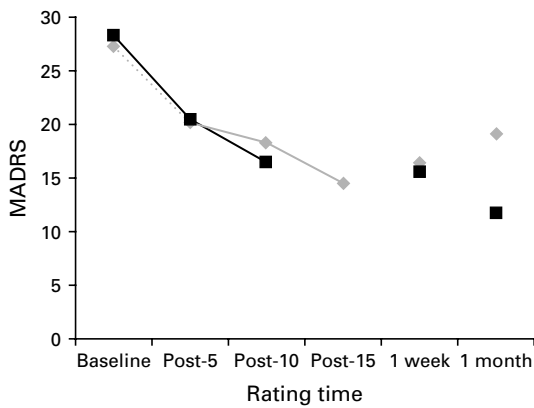


Fig. 2. Mean Montgomery-Asberg Depression Rating Scale (MADRS) scores for active and sham treatment groups over study duration. —◆—, Assignment to initial sham treatment; —■—, assignment to active treatment. Dotted part of grey line (.....) denotes initial period of sham treatment. Solid grey line (—) indicates delivery of active treatment. Therefore the sham group initially received five sham treatments followed by ten active treatments. The active group received ten active treatments throughout.

antidepressants, also did not find any significant time \times group interactions.

Over the first ten treatment sessions, there was a significant difference between baseline and post-10 scores on all measures: HAM-D₁₇ ($F=30.95$, d.f.=33, $p=0.00$), MADRS ($F=54.40$, d.f.=33, $p=0.00$), CGI ($F=29.53$, d.f.=32, $p=0.00$), BDI ($F=35.23$, d.f.=31, $p=0.00$), PGI ($F=46.23$, d.f.=33, $p=0.00$) but again there were no significant interactions between time and group. Over the first ten treatment sessions, six participants in the active treatment group met the criterion for response (defined as $\geq 50\%$ reduction in MADRS scores from baseline) and five met the criterion for remission (final score ≤ 10 on MADRS). In the sham treatment group, there were four responders and three remitters over the same time period.

Over the ten active treatment sessions, mean scores on MADRS decreased from 28.72 (s.d.=4.18) to 18.00 (s.d.=8.90) in the active treatment group, and from 22.45 (s.d.=8.09) to 14.47 (s.d.=10.04) in the group initially assigned to sham treatment. CORE scores did not correlate significantly with percentage change in MADRS scores over the ten active treatments for all subjects.

Neuropsychological functioning

Sham vs. active tDCS

Over the first five treatment sessions, a significant effect of time was found on COWAT letter total whereby

participants' performance was found to improve. In addition, a significant between-group effect was found on RAVLT learning (the active group having lower scores overall relative to sham) (see Table 3), but there were no significant time \times group interactions.

Analyses of participants' performance immediately before and after tDCS sessions 1 and 5 in the sham-controlled phase showed a significant effect of time on the SDMT at both time-points (performance improved in both the active and sham conditions), and on Choice RT after DCS 1 (both groups improved similarly). There were no significant time \times group interactions (see Table 4).

Effects of ten active DCS sessions on neuropsychological test performance

In the active group no significant changes were found across the following measures: RAVLT total ($F=0.37$, d.f.=16, $p=0.55$), RAVLT immediate ($F=1.09$, d.f.=16, $p=0.31$), RAVLT delay ($F=0.04$, d.f.=16, $p=0.85$), RAVLT learning ($F=0.02$, d.f.=16, $p=0.89$), TMT A ($F=0.62$, d.f.=16, $p=0.44$), Digit span forwards ($F=0.88$, d.f.=16, $p=0.36$), COWAT letter ($F=2.92$, d.f.=16, $p=0.11$), and COWAT category ($F=0.24$, d.f.=16, $p=0.63$). Improvements in performance were found on Digit span backwards ($F=6.57$, d.f.=16, $p=0.02$) and TMT B ($F=5.01$, d.f.=16, $p=0.04$).

Similarly, in the group which commenced with sham tDCS but went on to receive ten active treatment sessions, no significant changes were found following the active treatment phase on the following measures: RAVLT immediate ($F=0.06$, d.f.=13, $p=0.81$), RAVLT delay ($F=0.43$, d.f.=13, $p=0.52$), RAVLT learning ($F=0.09$, d.f.=13, $p=0.77$), TMT A ($F=0.05$, d.f.=13, $p=0.83$), TMT B ($F=0.79$, d.f.=12, $p=0.39$), Digit span forwards ($F=0.99$, d.f.=13, $p=0.34$), Digit span backwards ($F=0.08$, d.f.=13, $p=0.78$), COWAT letter ($F=0.03$, d.f.=13, $p=0.86$), and COWAT category ($F=0.45$, d.f.=13, $p=0.51$). Participants' performance in this group improved on RAVLT total ($F=8.35$, d.f.=13, $p=0.01$).

Adverse outcomes and side-effects

One participant in the sham treatment group committed suicide the day after receiving the first active treatment session. No clinical changes, including negative emotional reactions, had been apparent after the active treatment session. The timing of the suicide coincided with the single occasion when he was briefly left alone, as he had been continuously in the company of family members during the preceding few weeks.

Table 2. Mood ratings over sham-controlled period (first five treatment sessions): sham *vs.* active

Scale	Group, means (s.d.)										
	Baseline		Post-DCS 5		d.f.	Active <i>vs.</i> sham		Time effects		Time × group interaction	
	Sham	Active	Sham	Active		<i>F</i>	<i>p</i>	<i>F</i>	<i>p</i>	<i>F</i>	<i>p</i>
HAMD-17	17.25 (4.70)	18.30 (5.75)	13.50 (5.45)	15.43 (6.69)	38	0.83	0.34	19.31	0.00	0.34	0.57
MADRS	28.40 (4.44)	29.20 (4.87)	22.45 (8.09)	23.60 (7.72)	38	0.30	0.59	31.18	0.00	0.03	0.87
CGI	4.40 (0.68)	4.26 (0.65)	3.90 (0.91)	3.87 (0.78)	37	0.17	0.68	10.98	0.00	0.15	0.70
BDI	26.89 (9.88)	27.80 (8.02)	21.25 (12.25)	21.88 (8.42)	36	0.07	0.80	31.73	0.00	0.02	0.89
PGI	4.00 (0.00)	4.05 (0.22)	3.45 (0.83)	3.58 (0.85)	38	0.41	0.53	14.96	0.00	0.08	0.78

DCS, Direct current stimulation; HAMD₁₇, 17-item Hamilton Depression Rating Scale; MADRS, Montgomery–Asberg Depression Rating Scale; CGI, Clinician Global Impressions; CORE, CORE Measure of Psychomotor Disturbance; BDI, Beck Depression Inventory; PGI, Patient Global Impressions.

Table 3. Cognitive test results over five-session blind period: sham *vs.* active

	Group, means (S.E.M.)										
	Baseline		Post-DCS 5			Active <i>vs.</i> sham		Time effects		Time × group interaction	
Measure	Sham	Active	Sham	Active	d.f.	<i>F</i>	<i>p</i>	<i>F</i>	<i>p</i>	<i>F</i>	<i>p</i>
RAVLT											
Total	50.39 (2.56)	54.41 (2.56)	51.76 (2.43)	54.05 (2.43)	37	0.91	0.35	0.01	0.91	0.44	0.51
Immediate	10.40 (0.75)	11.30 (0.75)	9.98 (0.84)	11.22 (0.80)	37	1.05	0.31	0.08	0.78	0.21	0.65
Delay	10.62 (0.68)	11.53 (0.68)	10.05 (0.72)	11.15 (0.72)	37	1.16	0.29	1.50	0.23	0.62	0.81
Learning	6.55 (0.45)	4.75 (0.45)	6.52 (0.53)	5.88 (0.53)	37	5.37	0.03*	1.24	0.27	1.64	0.21
Trail Making Test											
Part A	47.08 (3.21)	42.93 (3.21)	44.89 (2.95)	38.67 (2.95)	37	1.64	0.21	0.71	0.41	0.37	0.55
Part B	79.69 (6.42)	66.70 (6.25)	75.75 (4.91)	65.09 (4.78)	36	2.53	0.12	1.37	0.25	0.15	0.70
Digit Span											
Forward	7.98 (0.57)	8.52 (0.57)	8.68 (0.53)	8.68 (0.53)	37	0.15	0.70	2.28	0.14	0.65	0.43
Backward	6.72 (0.50)	7.43 (0.50)	7.39 (0.55)	7.06 (0.55)	37	0.08	0.78	1.11	0.30	2.63	0.11
COWAT											
Letter	35.51 (2.73)	40.09 (2.73)	40.57 (2.71)	43.93 (2.71)	37	1.15	0.29	8.87	0.01*	0.27	0.61
Category	20.14 (1.12)	21.41 (1.12)	17.46 (1.37)	22.39 (1.37)	37	4.02	0.05	0.58	0.45	4.23	0.05

DCS, Direct current stimulation RAVLT, Rey Auditory Verbal Learning Task; COWAT, Controlled Oral Word Association Test. All analyses control for percentage change in Montgomery–Asberg Depression Rating Scale score from baseline.

* $p \leq 0.05$.

Suicidal thoughts had been present for months, although the risk of suicide had not been rated as high, and had been noted and closely monitored during the sham-controlled phase, by both the treating psychiatrist and study psychiatrist. There were no other serious adverse outcomes.

Side-effects occurring during active treatment were mild to moderate skin redness ($n=32$), itchiness ($n=13$) or tingling ($n=6$) at the electrode sites (primarily at the anode), mild headache ($n=8$), light-headedness ($n=4$), ringing in the ears ($n=3$), blurred vision ($n=2$), brighter or illuminated vision ($n=2$),

Table 4. Cognitive test results immediately before and after tDCS sessions 1 and 5: sham *vs.* active

Measure	Group means (S.E.M.)										
					d.f.	Active <i>vs.</i> sham		Time effects		Time × group interaction	
	Pre-DCS		Post-DCS			<i>F</i>	<i>p</i>	<i>F</i>	<i>p</i>	<i>F</i>	<i>p</i>
	Sham	Active	Sham	Active							
DCS 1											
SDMT	46.95 (2.37)	50.20 (2.37)	54.70 (2.81)	55.80 (2.81)	38	0.37	0.55	62.56	0.00**	1.62	0.21
Simple RT	0.28 (0.01)	0.28 (0.01)	0.28 (0.01)	0.28 (0.01)	37	0.00	0.95	0.71	0.40	0.12	0.73
Choice RT	0.62 (0.02)	0.62 (0.02)	0.58 (0.02)	0.59 (0.02)	35	0.08	0.78	14.66	0.00**	0.16	0.70
DCS 5											
SDMT	52.95 (2.73)	55.50 (2.98)	60.16 (3.43)	62.38 (3.74)	33	675.52	0.00**	38.00	0.00**	0.02	0.88
Simple RT	0.27 (0.01)	0.28 (0.01)	0.28 (0.01)	0.28 (0.01)	33	0.05	0.83	0.01	0.91	0.87	0.36
Choice RT	0.58 (0.03)	0.65 (0.03)	0.57 (0.03)	0.63 (0.03)	31	2.34	0.14	2.52	0.12	0.08	0.78

tDCS, Transcranial direct current stimulation; SDMT, Symbol Digit Modalities Test; RT, reaction time.

** $p \leq 0.01$.

tingling in face/body ($n=2$), transient hypomania ($n=1$) (see Arul-Anandam *et al.* 2009a), alleviation of neuropathic pain ($n=1$) (see Arul-Anandam & Loo, 2009b), reduced concentration ($n=1$), slight 'eyelid jolt' ($n=1$), nausea ($n=1$), mild euphoria ($n=1$), disorientation ($n=1$), transient tiredness ($n=1$), constriction when swallowing ($n=1$), insomnia ($n=1$) and anxiety ($n=1$). Side-effects occurring during sham treatment were mild redness ($n=12$), tingling ($n=8$) or itchiness ($n=7$) at the electrode sites, mild headache ($n=6$), nausea ($n=2$), light-headedness ($n=2$), clearer vision ($n=1$) and a pulsating sensation at the start ($n=1$). In both groups some subjects experienced multiple side-effects.

Integrity of blinding

When asked to guess their treatment group at the end of the ten-session double-blind phase, responses of the active group were: active ($n=5$), sham ($n=7$), unsure ($n=5$). Sham group responses were: active ($n=7$), sham ($n=10$), unsure ($n=0$). The difference in active/sham guesses between the two groups was not significant ($\chi^2=0.00$, d.f.=1, $p=0.98$). Subjects were equally likely to base their guesses on either their change in mood or side-effects experienced.

Discussion

Unlike Fregni *et al.* (2006a), this study in a larger sample of patients did not find any difference between active and sham tDCS, despite using the same

treatment parameters (1 mA, 20-min stimulation, same electrode montage, five sessions given on alternate days). The response to active tDCS over ten treatment sessions is comparable to that reported by Boggio *et al.* (2008). In the Boggio *et al.* (2008) study, tDCS was given at a higher intensity (2 mA), for 20 min each weekday, over a 2-wk period, in an attempt to optimize efficacy. However, the magnitude of clinical improvement was no greater than that of the Fregni *et al.* (2006a) study, possibly because a treatment period of > 2 wk is necessary for a full antidepressant response, as seen in clinical trials of TMS (Loo & Mitchell, 2005).

Our results mainly differed from these two previous studies in that the same degree of improvement occurred in the group receiving sham treatment. There are several considerations relevant to this. First, approximately two thirds of the participants in the sham treatment group in our study were on concurrent antidepressant medications, whereas all subjects in the Boggio *et al.* (2008) study had been off antidepressant medications for at least 2 months prior to tDCS. While it is possible that this accounted for improvement during sham treatment in our study, this is unlikely, given that these were medications to which the participants had previously failed to respond. The medications were continued at stable doses due to concerns over clinical deterioration in the event of medication withdrawal. Second, the magnitude of improvement during sham treatment is comparable to that typically seen in antidepressant treatment trials (Walsh *et al.* 2002). Our sample was only moderately treatment resistant as judged by the number of antidepressant

medication trials failed prior to study enrolment (predominantly stages 0–III as defined by Thase & Rush, 1995), and a smaller placebo response may be expected if tDCS were trialled in a more treatment-resistant population. However, our sample had a similar level of treatment resistance to that of the Boggio *et al.* (2008) study. On the other hand, debriefing after the sham-controlled period confirmed our observations that subjects found it difficult to differentiate active and sham treatment, a factor that is likely to increase the placebo response. The difficulty of differentiating a true response from placebo response has also been evident in clinical trials of TMS in depression (Loo & Mitchell, 2005), possibly due to the raised expectations arising from these new brain stimulation technologies.

Apart from the issue of concurrent medications, our sample also differed from that of the Boggio *et al.* (2008) study in that patients with personality disorders were not excluded. Others have demonstrated that the presence of personality disorder reduced the likelihood of response to antidepressant treatment (Black *et al.* 1988). In other respects (age, gender ratio, depression severity), our sample was comparable to that of Boggio *et al.* (2008).

The CORE measure of psychomotor disturbance has been proposed as a predictor of response to other physical antidepressant treatments (e.g. electroconvulsive therapy, Hickie *et al.* 1996) but did not predict response to active treatment in this study.

tDCS given at 1 mA on alternate days over ten sessions was shown to be safe, with minor side-effects and no adverse effects on neuropsychological functioning. Given the circumstances of the suicide, it is unlikely that it was related to the single session of active tDCS stimulation, although this possibility cannot be excluded. Numerous other studies with anodal prefrontal and/or cathodal supraorbital stimulation at similar parameters have not reported negative emotional effects (e.g. Boggio *et al.* 2008; Fregni *et al.* 2005, 2006a; Kincses *et al.* 2004; Nitsche & Paulus, 2000). Improvements found in neuropsychological test performance were probably due to practice effects. These results are consistent with those of the clinical trial by Fregni *et al.* (2006b) and studies in which prefrontal tDCS at similar parameters in healthy volunteers was actually found to enhance neuropsychological function (Fregni *et al.* 2005; Kincses *et al.* 2004).

The main limitation of this study is that the sham-controlled period only spanned five treatment sessions given over 1½ wk. It is likely that a longer treatment period is necessary to distinguish true response from placebo effects which tend to be immediate but transient (Papakostas *et al.* 2006). Strengths of our study

include the detailed characterization of participants' depressive illness, and comprehensive assessments by blinded raters of the effects of tDCS on mood and neuropsychological function.

In conclusion, this study found that active tDCS had no adverse effects on neuropsychological function but was not superior to a robust placebo response, which occurred in the context of the excellent blinding that is possible with sham tDCS. Future studies may be more likely to demonstrate a difference between active and sham tDCS by the use of higher stimulation parameters (e.g. >1 mA current amplitude, daily treatment sessions) and testing tDCS in a more treatment-resistant sample.

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Statement of Interest

None.

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