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Research Report

A pilot study of alternative transcranial direct current stimulation electrode montages for the treatment of major depression

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ABSTRACT

Background: Typically, transcranial direct current stimulation (tDCS) treatments for depression have used bifrontal montages with anodal (excitatory) stimulation targeting the left dorsolateral prefrontal cortex (DLPFC). There is limited research examining the effects of alternative electrode montages.
Objective/hypothesis: This pilot study aimed to examine the feasibility, tolerability and safety of two alternative electrode montages and provide preliminary data on efficacy. The montages, Fronto-Occipital (F-O) and Fronto-Cerebellar (F-C), were designed respectively to target midline brain structures and the cerebellum.
Methods: The anode was placed over the left supraorbital region and the cathode over the occipital and cerebellar region for the F-O and F-C montages respectively. Computational modelling was used to determine the electric fields produced in the brain regions of interest compared to a standard bifrontal montage. The two montages were evaluated in an open label study of depressed participants ($N=14$). Mood and neuropsychological functioning were assessed at baseline and after four weeks of tDCS.
Results: Computational modelling revealed that the novel montages resulted in greater activation in the anterior cingulate cortices and cerebellum than the bifrontal montage, while activation of the DLPFCs was higher for the bifrontal montage. After four weeks of tDCS, overall mood improvement rates of 43.8% and 15.9% were observed under the F-O and F-C conditions, respectively. No significant neuropsychological changes were found.
Limitations: The clinical pilot was open-label, without a control condition and computational modelling was based on one healthy participant.
Conclusions: Results found both montages safe and feasible. The F-O montage showed promising antidepressant potential.

1. Introduction

Transcranial direct current stimulation (tDCS) is a neuromodulatory technique that involves the passing of a weak electric current to the brain through electrodes placed on the scalp. tDCS modulates cortical activity by polarising the resting membrane potential and influencing the likelihood of neurons firing (Bindman et al., 1964; Purpura and McMurtry, 1965). Studies in the motor cortex have demonstrated that anodal stimulation increases cortical excitability, whereas cathodal stimulation produces the opposite effect, diminishing cortical excitability (Nitsche and Paulus, 2000, 2001). If the stimulation is given at sufficient intensity and duration, effects lasting up to 90 min can be induced after a single session of tDCS (Nitsche and Paulus, 2000, 2001). Repeated stimulation sessions have also been shown to lead to cumulative changes in cortical excitability (Alonzo et al., 2012; Galvez et al., 2013). These principles underlie the therapeutic potential of tDCS which has been studied clinically as a treatment for illnesses and disorders associated with maladaptive cortical functioning (Arul-Anandam and Loo, 2009; Brunelin et al., 2012; Fregni et al., 2005). For example, it has been shown that anodal stimulation of the left dorsolateral prefrontal cortex (DLPFC) can improve symptoms of depression (Arul-Anandam and Loo, 2009; Brunoni et al., 2013; Kalu et al., 2012; Loo et al., 2012).

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A recent meta-analysis of randomised controlled trials has demonstrated that tDCS results in an average of 29% reduction in the severity of depressive symptoms after 5–15 treatment sessions (Kalu et al., 2012). However, a meta-analysis based on responder numbers failed to find a significant difference between active and sham stimulation (Berlim et al., 2013). Ongoing research efforts to increase the efficacy of tDCS for depression have focused on the use of higher "dosages". There has been a gradual increase in current intensities, stimulation duration and number of stimulation sessions used in clinical trials, though the size of the clinical effect to date has been relatively modest in treatment-resistant samples (Berlim et al., 2013; Blumberger et al., 2012; Kalu et al., 2012; Loo et al., 2012). In fact, a recent study examining excitability in the motor cortex of healthy participants found that longer stimulation durations and stronger current intensities do not necessarily result in greater excitability (Batsikadze et al., 2013), though the applicability of these findings to therapeutic uses in clinical populations is unknown. Further optimisation of stimulation parameters may include increases in stimulus parameters, although increases in current intensity and stimulus durations are limited by tolerability and the risk of skin damage (Rothwell, 2012). As such, alternative methods of optimising treatment efficacy, including alternative electrode montages, must also be considered.

Electrode montage determines current direction and electric field intensities in cerebral tissue (Bikson et al., 2012; Dmochowski et al., 2012). The standard electrode montage used in recent depression trials has involved placing the anode over the left dorsolateral prefrontal cortex (DLPFC; F3 on the 10-20 EEG system). This approach is based on research which suggests that this region has a key modulating role in depression, as treatments using transcranial magnetic stimulation (TMS) to increase activity in this region have been shown to be efficacious (George et al., 2010; O'Reardon et al., 2007; Slotema et al., 2010). The cathode is then either placed over the right supraorbital or lateral orbital (F8) area, or alternatively over the right DLPFC (F4) (Blumberger et al., 2012; Boggio et al., 2008; Brunoni et al., 2013; Fregni et al., 2006; Loo et al., 2012, 2010; Palm et al., 2012). Although to-date modern tDCS montages for depression have focused on anodal stimulation of the left DLPFC, evidence suggests that depression is a systems-wide disorder involving multiple cortical, subcortical and limbic brain regions (Anderson et al., 2012; Bora et al., 2012; Fox et al., 2012). Preliminary data suggests that tDCS given using alternative montages which more widely stimulate the cerebrum, including subcortical regions, may have greater efficacy (Martin et al., 2011).

Apart from the DLPFC, research interest has focused on regions such as the anterior cingulate cortex (ACC), in particular the subgenual ACC (sgACC), as well as the nucleus accumbens, insula, hippocampus, ventral capsule and striatum (Anderson et al., 2012; Fox et al., 2012; Mayberg, 2009). For example, imaging studies have demonstrated overactive metabolic activity in the sgACC, with normalisation following clinical response to treatment (Bewernick et al., 2010; Mayberg et al., 2000). Further, studies using the more invasive technique of deep brain stimulation (DBS) have demonstrated clinical efficacy through targeting the sgACC and other sub-cortical structures (Bewernick et al., 2010; Holtzheimer and Mayberg, 2012; Lozano et al., 2012; Malone et al., 2009). There is additionally increasing suggestion that the cerebellum may also play a role in emotion dysregulation and depressive pathophysiology (Fitzgerald et al., 2008; Hoppenbrouwers et al., 2008; Schutter and van Honk, 2005), thus offering another potential target for novel therapies. While originally thought only to be involved in motor function, the cerebellum is now thought to play a role in mood regulation through its functional and structural connections with the prefrontal cortex, brain stem and limbic structures (Beyer and Krishnan, 2002; Bostan et al., 2013; Konarski et al., 2005). Further, increased cerebral blood flow in the medial cerebellum and vermis have been associated with depression and have been found to decrease following successful treatment (Konarski et al., 2005; Videbech et al., 2001).

This pilot study aimed to examine the feasibility and safety of two alternative tDCS electrode montages (fronto-occipital, F-O; fronto-cerebellar, F-C), and provide preliminary data on the therapeutic potential of these two montages for the treatment of depression. The electrode montages were designed to target the midline and deep brain structures including the sgACC, nucleus accumbens and basal ganglia, while also delivering anodal left frontal stimulation. The rationale was that these electrode configurations would result in the greatest current flow through midline structures implicated in depression, with the F-C montage also aimed to modulate maladaptive cerebellar activity.

The clinical potential of these new montages was first tested by modelling the electric-fields (E-fields) that would result in key brain regions, and comparing this to our previously used F3–F8 montage (Loo et al., 2012, 2010). Following this, an open-label clinical pilot study of the montages was then conducted.

2. Method

2.1. Computational modelling

T1-weighted 3T MRI head scans of a healthy 35-year-old Asian male subject were obtained from Neuroscience Research Australia, and segmented into several tissue compartments using BrainSuite (Shattuck and Leahy, 2002) and ScanIP (Simpleware Ltd., UK) segmentation software. These tissue compartments included the skin, skull, cerebrospinal fluid (CSF), cerebrum, cerebellum and brainstem (Bai et al., 2014). The skull was further segmented into compact bone tissue (the innermost and outermost layers) and spongy bone tissue (the middle layer). The cerebrum was also segmented into grey matter and white matter. Several brain regions of interest (ROIs), considered important in tDCS therapeutic effects, were further segmented from the brain masks. ROIs examined were cerebellum, brain stem, bilateral DLPFC, bilateral orbitofrontal cortex (OFC), bilateral ACC and bilateral hippocampus. Most compartments of the head models were considered to be electrically homogeneous and isotropic, except the white matter. Electrical conductivities of the tissues can be found in Bai et al. (2014). All head compartments in the tDCS simulations were formulated as passive volume conductors using $\nabla \cdot (-\sigma \nabla \phi) = 0$, where ϕ is the electric potential, σ is the electric conductivity tensor, and ∇ is the del partial derivative operator given by $(\partial/\partial x, \partial/\partial y, \partial/\partial z)^T$. The electric field (E-field) vector was calculated from the negative gradient of potential according to $E = -\nabla\phi$. The model was solved using the COMSOL Multiphysics (v4.3a, COMSOL AB, Sweden) finite-element software package on a standard desktop PC with 24G RAM. Simulation results were analysed by comparing the average E-field magnitude $\overline{E}$ in several ROIs in the brain. Brain E-field distributions (magnitude and direction) with three montages were also investigated. For more detailed methodology, refer to Bai et al. (2014).

2.2. Electrode montages

As shown in Fig. 1, for F-O tDCS, the anode ($5 \times 7\ cm^2$) was placed horizontally over the left supraorbital region, using the AFz and FP1 positions on the 10-20 EEG system as the left and bottom edge boundaries of the electrode. The anode was over the left supraorbital region rather than in the centre of the forehead to avoid shunting of the current along the superior sagittal sinus (Neuling et al., 2012). The cathode was placed with the bottom edge over O1 and O2 ($10 \times 10\ cm^2$). A large cathode was used to reduce the cathodal effects of the stimulation and ensure broad stimulation of the midline structures. The anode was placed in the

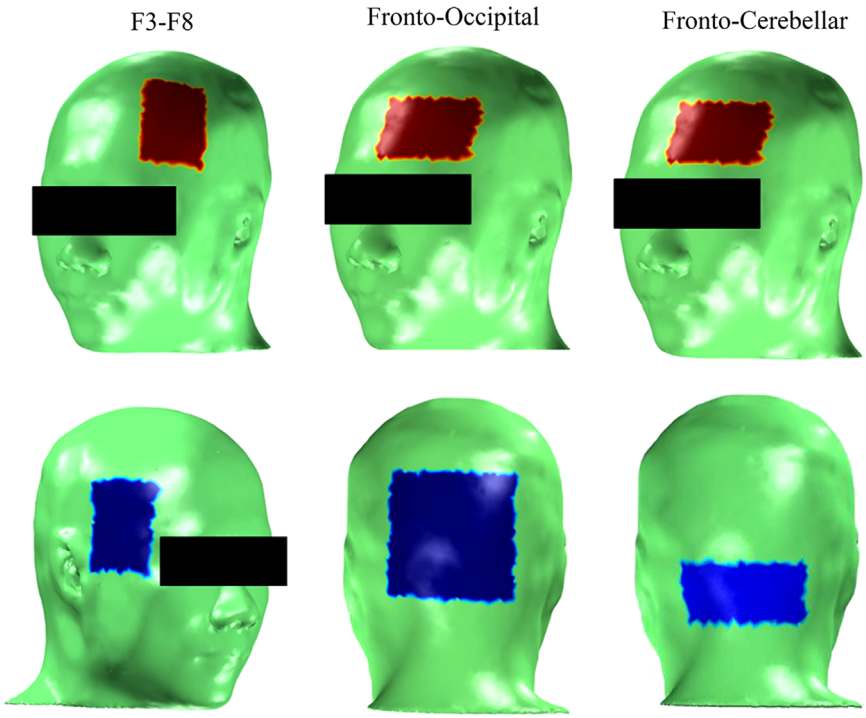

Fig. 1. tDCS electrode placement for the F3–F8, Fronto-Occipital and Fronto-Cerebellar montages. The red and blue electrodes represent the anode and cathode respectively. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

same position for the F-C montage while the cathode (5×10 cm^2) was placed horizontally with the top edge centered over the inion to achieve bilateral stimulation of the cerebellum. For the F3–F8 montage, standard 5×7 cm^2 electrodes were modelled.

2.3. Clinical pilot study of alternative tDCS montages

2.3.1. Participants

Fourteen participants with Major Depressive Disorder ($M=$ 44.86 years, 6 females) took part in this open-label study. Seven participants received F-O tDCS and seven participants received F-C tDCS. All participants met DSM-IV criteria for a Major Depressive Episode as assessed using the Mini International Neuropsychiatric Interview (Sheehan et al., 1998) and had a score of ≥ 20 on the Montgomery Åsberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979) at trial entry. Exclusion criteria included drug or alcohol abuse or dependence, co-morbid Axis-I disorders, neurological disorders, or failure to respond to electroconvulsive therapy in the current episode. Treatment resistance was assessed as the number of adequate trials of antidepressant medications failed during the current episode of illness, and also scored using the Maudsley Staging Method (Fekadu et al., 2009). Participants were either medication-free (F-O: $n=2$; F-C: $n=4$) or continued on antidepressant medications to which they had already failed to respond despite an adequate trial, with no change in dosages in the four weeks prior to the study and during the study. The study was approved by the Human Research Ethics Committee at the University of New South Wales. Written informed consent was obtained from participants prior to commencement of the study.

2.3.2. tDCS

tDCS was administered using an Eldith DC-Stimulator (NeuroConn GmbH, Germany) with conductive rubber electrodes covered by saline-soaked sponges, held in place by a band across the head. Stimulation was given at 2 mA for 20 min and the current was gradually ramped up and down at the start and end of the stimulation over 30 s. Electrode montages were as described above. Twenty sessions were administered on consecutive weekdays over four weeks. Further details of stimulation technique, including measures to avoid skin burns, are as previously described (Loo et al., 2011). Transient side effects immediately after the stimulation were also recorded.

2.3.3. Depression ratings

The primary outcome measure used to assess depression was MADRS. Participants were considered to have achieved response if there was a $\geq 50\%$ reduction in MADRS scores from baseline and remission if they achieved a MADRS of < 10. Ratings were completed by a psychologist or psychiatrist at baseline and after 8, 15 and 20 tDCS sessions. Participants were rated by the same rater at each time point and raters were aware of the electrode montage and open-label nature of the study.

2.3.4. Neuropsychological assessment

Neuropsychological functioning was assessed at baseline and after 20 tDCS sessions. The battery of tests used was identical to those of the Loo et al. (2012) study and was chosen to examine performance of memory and frontal lobe functions. The tests administered included the Rey Auditory Verbal Learning Test (RAVLT; Rey, 1964), Digit Span (Wechsler, 1981, 1997), Letter Number Sequencing (LNS; Wechsler, 1997), Stroop Test (Regard, 1981), and Controlled Oral Word Association Test (COWAT; Benton and Hamsher, 1989). Acute cognitive effects of tDCS were also assessed immediately before and after treatments 1 and 20 by administration of the Symbol Digit Modalities Test (SDMT; Smith, 1991) and simple and choice reaction-time (RT) tests. Alternative forms were used for the RAVLT, COWAT, and SDMT to minimise practice effects.

2.3.5. Data analysis

Demographic and clinical differences between the two groups were examined using a one-way analysis of variance (ANOVA) for continuous variables and the Fisher's exact test for categorical variables. A repeated measures ANOVA was conducted on MADRS scores for each treatment group, with one within-subjects factor of time (baseline, post 8, post 15, and post 20). The Greenhouse-Geisser correction was applied if Mauchley's assumption of sphericity was violated. Where ratings were not completed, values from the previous rating point were carried forward. For acute cognitive effects, paired-samples *t* tests (two-tailed) were conducted to compare differences immediately before and after the first and last session. Paired-sample *t*-tests were also conducted to examine performance changes on the neuropsychological tests from baseline to post treatment. Statistical significance was set at $p < .05$.

3. Results

3.1. Computational modelling

The electric field ($\overline{E}$) in the whole brain was similar for the three montages (0.080–0.087 V/m), suggesting that there were no differences in the degree of shunting of current over the scalp. Fig. 2 shows the E field in brain regions of interest: DLPFC, ACC, and cerebellum. As shown in Fig. 2, there was greater E field in bilateral DLPFCs for the F3–F8 montage than the two alternative montages. In contrast, the alternative montages tended to result in greater E field in the left ACC and cerebellum as compared to the F3–F8 montage. Overall, the two alternative montages produced a similar pattern of activation though the F-C montage produced stronger E-field in the cerebellum than the F-O montage.

There were no differences in baseline clinical and demographic variables between participants receiving the two montages ($p > .05$). The baseline data for the two groups are presented in Table 1. One participant in the F-O condition was withdrawn after 13 sessions due to clinical deterioration and one participant in F-C withdrew after 12 sessions due to lack of improvement.

3.2. Depression ratings

Mean MADRS ratings for the two montages across time are shown in Fig. 3. For F-O tDCS, there was a significant reduction in mean depression scores over the course of treatment (end treatment score compared to baseline score, $F(3, 18) = 12.62$, $p < 0.001$). Four of seven participants achieved response following the course of treatment including one participant who achieved remission. For F-C tDCS, there was a slight reduction in mean MADRS scores after four weeks of treatment compared to baseline, but the change was not statistically significant, $F(3, 18) = 1.92$, $p = 0.16$. One of the seven participants achieved response and none reached remission.

3.3. Cognitive outcomes

Analysis of acute cognitive effects (i.e., comparing results immediately before and after a single tDCS session) showed an improvement in performance on the SDMT after the first session of F-O tDCS (see Table 2). No other acute effects were found after Sessions 1 and 20 for the two montages.

All but two participants (who withdrew prior to session 20) completed neuropsychological testing before and after four weeks of tDCS. As shown in Table 3, for both montages there were no significant changes in performance on the neuropsychological tests from baseline to post treatment.

3.4. Side effects

During tDCS, participants reported the following sensations: tingling (F-O $n=7$, F-C $n=6$), burning (F-O $n=7$, F-C $n=6$), itching (F-O $n=3$, F-C $n=2$) and pain (F-O $n=2$, F-C $n=2$). After tDCS, all participants showed redness of skin at the electrode sites (subjectively rated by tDCS administrator). Other side effects reported include feeling lightheaded or dizzy (F-O $n=4$, F-C $n=2$), headache (F-O $n=4$, F-C $n=3$), nausea (F-O $n=1$, F-C $n=2$) and fatigue (F-O $n=1$, F-C $n=0$). All side effects reported were transient without requiring intervention and the majority were of a mild to moderate intensity.

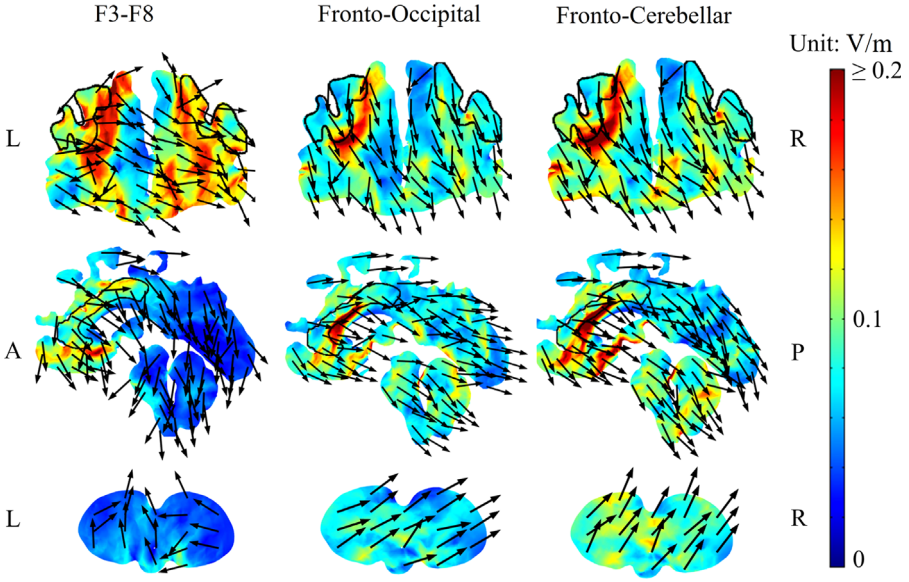

Fig. 2. Cross sectional slices for the F3–F8, Fronto-Occipital and Fronto-Cerebellar montages. From top to bottom, the slices show the coronal slice through the dorsolateral prefrontal cortex, the sagittal slice through the anterior cingulate cortex and the horizontal slice showing the cerebellum. The black outlines indicate regions of interest: dorsolateral prefrontal cortex (top slice), anterior cingulate cortex (middle slice), cerebellum (bottom slice). "A", "P", "L" and "R" represent "anterior", "posterior", "left" and "right" respectively.

Table 1
Baseline participant demographic and clinical data for Fronto-Occipital and Fronto-Cerebellar tDCS.

Montage	Baseline demographics	
	Fronto-Occipital ($n=7$)	Fronto-Cerebellar ($n=7$)
Age *M* (SD), years	45.8 (9.47)	45 (10.03)
Age at onset *M* (SD), years	20 (5.62)	28.86 (11.58)
Gender, females *n*	3	3
Number of participants on concurrent antidepressants *n*	6	3
Number of antidepressants failed during the current episode *M* (SD)	1.88 (1.89)	1.14 (1.51)
Treatment resistance – Maudsley score *M* (SD)	7.38 (2.77)	6.33 (2.07)
Presence of melancholia *n*	5	4
Duration of current episode *M* (SD), months	22.08 (19.45)	17.64 (23.47)
Duration of previous episodes *M* (SD), months	56 (50.75)	90.5 (53.09)
MADRS *M* (SD)	33.57 (8.96)	28.71 (3.86)

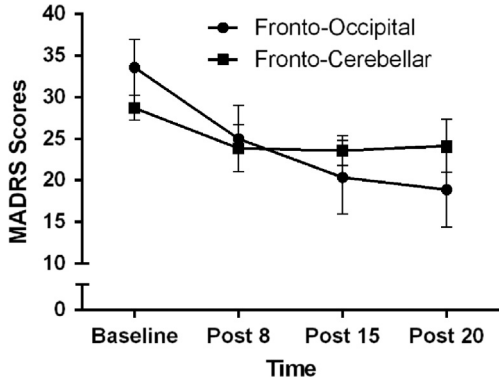

Fig. 3. Average scores on the Montgomery Åsberg Depression Rating Scale (MADRS) across time for Fronto-Occipital and Fronto-Cerebellar treatment groups.

4. Discussion

This study found that after four weeks of treatment with the F-O montage, there was a 43.8% reduction in the clinician-rated MADRS scores. This change in depression scores is comparable to that reported in a prior study of open label fronto-extracephalic tDCS using identical treatment parameters (Martin et al., 2011) as well as results of open label studies of repetitive transcranial magnetic stimulation (rTMS) (Avery et al., 2008; Burt et al., 2002). Other open-label trials of tDCS using a bifrontal montage have reported approximately 20% improvement in mood scores, though these studies gave a lower number of treatment sessions (10 sessions *vs.* 20 sessions in this study), which may account for the lesser degree of improvement (Brunoni et al., 2011b; Dell'Osso et al., 2012; Ferrucci et al., 2009).

Computer modelling further showed that the F-O montage resulted in less E-field bilaterally in the DLPFC as compared to the typically used bifrontal F3–F8 montage. This suggests that anodal stimulation of the left DLPFC may not be the critical component that is required for antidepressant response to tDCS. The F-O montage resulted in greater stimulation of the ACC, and antidepressant efficacy with this montage supports findings of DBS studies which show that stimulation of the sgACC and the neighbouring basal ganglia regions is effective at reducing symptoms of depression (Bewernick et al., 2010; Lozano et al., 2012; Malone et al., 2009).

A relatively smaller level of reduction in depressive symptoms was observed following F-C tDCS, with no significant change in overall MADRS scores found from baseline. In fact, the improvement in depressive symptoms seen (15.9%) was similar to that of sham stimulation in double-blinded RCTs (10–19%) (Kalu et al., 2012). Given that the F-C montage results in similar stimulation of the ACC to the F-O montage, one possible explanation for the difference in efficacy seen is that cerebellar stimulation in the F-C montage negated beneficial antidepressant effects of frontal anodal tDCS.

The F-C montage was specifically designed to deliver cathodal cerebellar stimulation, in order to test the hypothesis that cathodal stimulation of the cerebellum should correct cerebellar overactivity (Nitsche and Paulus, 2000, 2001; Nitsche et al., 2005), thereby producing an antidepressant response (Konarski et al., 2005, Videbech et al., 2001). However, an additional consideration is that placement of the cathode over the cerebellum may not simply have resulted in inhibitory effects. The actual effect on each neuron (whether excitatory or inhibitory) may depend on the orientation of that neuron in relation to the electric field direction. This will in turn be affected by the overall neuroanatomical structure of the cerebral tissue stimulated, e.g. effects of cortical folding. (Datta et al., 2009; Purpura and McMurtry, 1965; Radman et al., 2009). Results showed that there were not only differences in electric field intensity, but in electric field direction between the three montages, in the regions of interest. Thus, it is uncertain whether cerebellar stimulation in this study was overall excitatory or inhibitory, but nevertheless, these preliminary results suggest that it may not have contributed towards an antidepressant response. This is consistent with the results of others, who found that cerebellar stimulation enhanced emotional recognition of negative emotions, regardless of stimulation polarity (Ferrucci et al. 2012). While the difference in clinical outcomes between the two montages is likely due to different electrode placements, it must also be noted that different sized cathodes were used in the two montages. This may have also influenced the clinical outcomes observed as electrode size and current density have been found to modulate levels of cortical excitability (Bastani & Jaberzadeh, 2013).

Both the electrode montages were found not to result in any significant changes in neuropsychological functioning after four weeks of treatment. This is similar to findings from previous trials of other tDCS montages for depression where tDCS was either found to improve or have no effect on cognition (Brunoni et al., 2013; Ferrucci et al., 2009, 2012; Loo et al., 2012). Interestingly, F-O tDCS led to acute improvement in psychomotor speed immediately following the first treatment, as assessed by SDMT. With F-C tDCS this finding was similarly at trend significance. These results are in accordance with a recent sham-controlled study using frontal tDCS which was conducted under blinded conditions (Loo et al. 2012). Parallel test forms were administered in both studies, suggesting that these findings were not due to practice effects. Computer modelling showed that all three tDCS electrode montages result in diffuse stimulation, predominately in left frontal cortical and subcortical, and subcortical temporal areas. Anodal tDCS when given to the motor cortex has been demonstrated to increase cortical excitability in the period immediately following stimulation

Table 2
Cognitive outcomes (group means, standard deviations) for acute effects, tested immediately before and after tDCS Sessions 1 and 20.

	Variable	Pre-DCS	Post-DCS	*t*	df	*p*
		M (SD)	*M* (SD)			
Fronto-Occipital						
Session 1	SDMT	51.33 (3.3(3)	57.00 (5.80)	−3.08	5	0.03
	Simple RT	0.30 (0.06)	0.30 (0.06)	−0.02	5	0.98
	Choice RT	0.65 (0.15)	0.59 (0.08)	1.66	5	0.16
Session 20	SDMT	53.80 (7.92)	57.00 (9.00)	−1.5	4	0.21
	Simple RT	0.29 (0.07)	0.30 (0.03)	−0.43	5	0.69
	Choice RT	0.58 (0.08)	0.60 (0.10)	−1.16	5	0.30
Fronto-Cerebellar						
Session 1	SDMT	47.8 (10.94)	52.8 (10.33)	−2.28	4	0.085
	Simple RT	0.27 (0.04)	0.30 (0.05)	−1.66	5	0.158
	Choice RT	0.64 (0.08)	0.63 (0.08)	0.52	5	0.623
Session 20	SDMT	53.8 (7.91)	54.0 (9.61)	−0.12	5	0.908
	Simple RT	0.27 (0.02)	0.30 (0.04)	−1.86	5	0.122
	Choice RT	0.58 (0.16)	0.57 (0.13)	0.78	5	0.469

Abbreviations: Symbol Digit Modalities Test (SDMT); Reaction Time (RT).

Table 3
Neuropsychological outcomes (group means, standard deviations) at baseline and after 20 sessions of tDCS.

Montage	Variable	Baseline *M* (SD)	Post 20 *M* (SD)	*t*	df	*p*
Fronto-Occipital	RAVLT	53.83 (13.96)	53.00 (8.88)	0.27	5	0.80
	Digit span	17.83 (6.94)	17.67 (8.66)	0.1	5	0.92
	LNS	12.00 (3.41)	12.17 (4.07)	−0.16	5	0.88
	COWAT	45.50 (14.38)	42.83 (15.88)	0.91	5	0.41
	Stroop interference	20.93 (5.37)	19.84 (5.53)	0.80	4	0.47
Fronto-Cerebellar	RAVLT	54.6 (12.0)	49.3 (18.4)	2.0	5	0.11
	Digit Span	18.2 (4.9)	18.5 (4.8)	−0.67	5	0.53
	LNS	18.3 (4.2)	12.3 (4.0)	−0.81	5	0.46
	COWAT	42.8 (12.2)	48.8 (11.2)	−2.12	5	0.09
	Stroop interference	22.9 (8.4)	21.8 (7.2)	0.36	5	0.73

Abbreviations: Rey Auditory Verbal Learning Test (RAVLT); Letter Number Sequencing (LNS); Controlled Oral Word Association Test (COWAT).

(Nitsche and Paulus, 2000, 2001). Speculatively, it is possible that improved cognitive performance immediately following tDCS may therefore have been due to enhanced neural transmission between these interconnected regions, resulting in faster learning on the task.

The side effects reported during and after stimulation were similar to those typically reported in other tDCS studies (Brunoni et al., 2011a). The incidence of side effects was comparable to that of our prior study of bifrontal tDCS, which used similar stimulation parameters (Loo et al., 2012).

There are several important limitations to this study. The clinical pilot was open-label, without a control condition. Participants and raters were aware that active stimulation was being administered during the course of treatment and this may have contributed to a placebo effect, though one would expect that both the F-O and F-C conditions would have been affected by this equally. However, given the small sample size, no definitive conclusions can be drawn about the therapeutic potential of the F-C montage. Further, participants were not randomly allocated to the two montages, precluding any direct comparison between the montages.

Computer modelling was based on the head of one healthy participant. It is possible that the nature and magnitude of electric field alterations with variation of montage may differ between individuals, due to differences in head and brain anatomy. It has also been shown previously that there may be structural differences in the brain between healthy individuals and individuals with mood disorders (Drevets et al., 2008). However, a previous study which systematically modelled multiple electrode montages, including the montages used in this clinical study, in both a healthy individual and a depressed individual, found minimal differences in the pattern of E-field distributions (Bai et al., 2014). It would have been interesting to correlate the present model predictions with clinical improvement on an individual participant basis. However, with the current methodology, this would be a very labour-intensive and expensive exercise, given the requirement for individual MRI scans and the extensive labour involved in the detailed segmentation required to prepare each head model with the level of anatomical detail shown in this study.

Overall, the results of this open-label pilot clinical trial suggest that the F-O and F-C tDCS montages were safe and well tolerated. Our results suggest the F-O montage may have promising antidepressant potential, though the clinical efficacy of the F-C montage remains as yet unclear. These pilot results should be followed up by randomised clinical trials directly comparing these electrode montages to the more commonly used bifrontal montage, and also to a sham stimulation condition. A further line of investigation would be to trial tDCS with the F-O montage in depressed participants who do not respond to bifrontal tDCS, given the different pattern of brain activation involved in these two montages.

Conflict of interest

Authors KAH, DM, AA and CKL are conducting another clinical trial of tDCS, using equipment provided by the Soterix company. This trial is funded by a competitive research grant (to CKL) from the Stanley Medical Research Foundation. CKL has also received a research grant from the Australian Health and Medical

Research Council to conduct a clinical trial of tRNS, a related technology, in depression. CKL reports no other biomedical financial interests or potential conflicts of interest.

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