Frontal Cortex Stimulation Reduces Vigilance to Threat: Implications for the Treatment of Depression and Anxiety

Supplemental Information

Supplemental Methods and Materials

Participants
Participants were recruited using print and online advertisements. They were reimbursed for their time and travel expenses at a rate of £10 per hour. Exclusion criteria included any history of a psychological disorder, any psychoactive medication in the last three months, any family history of bipolar disorder and any other contraindications to transcranial direct current stimulation (tDCS). We specifically excluded a familial history of bipolar disorder as a precaution because case studies in the literature have reported potential induction of a manic state with tDCS (1-3). An initial screening session was carried out at the Warneford hospital. After informed consent was obtained, participants were screened using the structured clinical interview for DSM IV disorders to rule out any current or prior axis I and II conditions. In addition, participants were asked to complete the Eysenck Personality Questionnaire and the National Adult Reading Test.

Transcranial Direct Current Stimulation
In the sham condition participants received 30 sec of direct current, followed by impedance control with a small current pulse every 550 ms (110 μA over 15 ms) instead of the stimulation current, resulting in an instantaneous current of not more than 2 μA. This method of sham stimulation produced the physical sensations typical of active tDCS and, in addition, allowed for effective double blinding by displaying realistic impedance values on the device display (4). The experimenter was thus blind to the stimulation condition, facilitated by a
‘study’ mode for blinding on the device. By necessity, the experimenter was not blind to the electrode montage (bipolar-balanced versus unbalanced), but as part of the blinding procedure sham tDCS was applied using a bipolar-balanced montage in half the participants while the other half received the bipolar-unbalanced montage.

**Mood Questionnaire Measures**

Participants filled out baseline mood questionnaires, including the Beck Depression Inventory (BDI) (5), Positive and Negative Affective Schedules (PANAS) (6) and a Visual Analogue Scale (VAS) of emotions (happy, sad, hostile, alert, anxious, calm). The PANAS and VAS measures were repeated after stimulation. The questionnaires were included as a control measure, as there was no *a priori* expectation of acute mood changes resulting from tDCS.

**Behavioral Measures**

In brief, facial expressions associated with six emotions (anger, disgust, fear, happiness, sadness, surprise) were presented on a computer screen. Using computer graphic techniques, these expressions were averaged in 10% steps between 10% and 100% emotion (40 examples of each emotion were presented over 15 minutes). Each of the 10 actors was also presented while showing a neutral facial expression. Each stimulus remained on the screen for 500 ms, after which the volunteers responded by pressing labeled keys. This task was programmed in bespoke stimulus presentation software (University of Oxford) and was competed roughly 2 minutes after the tDCS stimulation ended.

To assess emotional categorization, 60 personality characteristics selected to be extremely likable or unlikable (7) were presented on the computer screen for 500 ms (matched on word length, frequency, and meaningfulness), for a total task time of 5 minutes.
The volunteers were asked to categorize these personality traits as likable or unlikable as quickly and as accurately as possible using a key press. This task was programmed in bespoke stimulus presentation software (University of Oxford) and was completed 15-20 minutes after the tDCS stimulation ended.

Finally, emotional memory was examined by a surprise test of recall of the personality traits used in the emotional categorization task, 15 minutes after task completion. The number of items recalled for each valence (minus false positives) in a two minute period was calculated. This task was completed 35-40 minutes after the tDCS stimulation ended.

Calculations and Statistics

Mean accuracy scores and reaction times (RTs) were calculated for each individual for each emotion in the facial expression recognition task (neutral, anger, disgust, fear, happy, sad and surprise) and for each valence (positive and negative) in the emotional categorization and memory tasks. Performance on the dot-probe task was characterized by an index of emotional vigilance, i.e., mean RT difference between the two stimulus pair types (fear vigilance = neutral - fear, happy vigilance = neutral - happy). For all tasks, RTs were calculated based only on correct trials and outliers were removed (i.e., RTs < 200 ms or > 1200 ms, or RTs +/- 3 SD from an individual participant’s mean). Outlier removal resulted in < 3% of data being removed on any task. Since the goal of the study was to test whether either of the two DLPFC stimulation montages changed emotional processing compared to normal, the data from each of the tasks were analyzed using analysis of variance (ANOVA), with tDCS condition (bipolar-balanced, bipolar-unbalanced, sham) as the between-subjects variable and the relevant task measures as within-subjects variables. Significant main effects or interactions involving tDCS were further investigated using planned contrasts of each of the two active tDCS conditions against sham. Multiple comparisons were corrected for within-tasks but not
between-tasks. Sphericity violations were corrected using the Huynh-Feldt procedure. The experimenter remained blinded until the main analysis had been completed. Analyses were conducted using IBM SPSS Statistics 20.

Supplemental Results

Group Matching

Baseline sub-clinical levels of depression (measured with the BDI) did not differ between the groups ($F_{(2,57)} = .235, p = .792$). Baseline mood scores on the PANAS and VAS also did not differ between the groups (PANAS: $F_{(2,52)} = 1.453, p = .243$; VAS: $F_{(6,150)} = .677, p = .660$).

Mood Questionnaire Measurements

PANAS Change. Change scores (post – pre) were analyzed using rm-ANOVA with tDCS (active bipolar-balanced, active bipolar-unbalanced, sham) as a between-subjects variable and valence (positive, negative) as a within-subjects variable. There were no statistically significant main effects of tDCS ($F_{(2,56)} = .480, p = .621$) or valence ($F_{(1,56)} = .233, p = .632$) and the two-way tDCS × valence interaction was also not significant ($F_{(2,56)} = .377, p = .688$) (see Table 1). Therefore, as expected, stimulation did not significantly alter the PANAS affect measure.

VAS Change. An rm-ANOVA was carried out on the VAS emotion change scores with tDCS (active bipolar-balanced, active bipolar-unbalanced, sham) as a between-subjects variable and emotion (happy, sad, hostile, alert, anxious, calm) as a within-subjects variable. There was a statistically significant main effect of tDCS ($F_{(2,56)} = 3.933, p = .025$), with the active tDCS groups showing a net reduction in VAS scores across all emotions (positive and negative) compared to the sham group, who showed a net increase in VAS scores across all emotions. There was also a statistically significant effect of emotion ($F_{(8,156.4)} = 3.073, p = .033$), with
overall reductions in anxiety and increases in calmness and happiness across all three groups. However, there was no significant two-way tDCS × emotion interaction ($F_{(5.6, 156.4)} = .500, p = .795$) and therefore, as expected, stimulation did not significantly alter specific VAS emotion change scores.

**Behavioral Measurements**

*Facial Expression Recognition Task.* Rm-ANOVAs were carried out on percent correct, reaction times and misclassifications, with tDCS (active bipolar-balanced, active bipolar-unbalanced, sham) as a between-subjects variable and emotion (neutral, anger, disgust, fear, happiness, sadness, surprise) as a within-subjects variable. There were no statistically significant main effects of tDCS on percent correct ($F_{(2,56)} = .119, p = .888$), reaction times ($F_{(2,56)} = 1.756, p = .182$) or misclassifications ($F_{(2,56)} = .183, p = .833$). There were significant main effects of emotion, on percent correct ($F_{(6,336)} = 117.432, p < .001$), reaction times ($F_{(5,278.2)} = 10.031, p < .001$) and misclassifications ($F_{(1.92,107.7)} = 216.732, p < .001$), reflecting higher accuracy, faster reaction times and lower misclassifications for happy faces compared to other emotions across all stimulation conditions. However, there were no significant two-way tDCS × emotion interactions, not for percent correct ($F_{(10,290)} = .314, p = .979$), reaction times ($F_{(9,245)} = .870, p = .550$) or misclassifications ($F_{(4,101)} = .583, p = .658$).

Therefore, tDCS did not significantly alter facial expression recognition.

*Emotional Categorization/ Memory Task.* Rm-ANOVAs were carried out on reaction time and recall data with tDCS (active bipolar-balanced, active bipolar-unbalanced, sham) as a between-subjects variable and valence (positive, negative) as a within-subjects variable. There were no statistically significant main effects of tDCS on reaction times ($F_{(2,55)} = .939, p = .397$) and recall ($F_{(2,55)} = .617, p = .543$). There were significant main effects of valence on reaction times ($F_{(1.55)} = 31.160, p < .001$) and recall ($F_{(1.55)} = 11.573, p = .001$), reflecting
faster reaction times and greater recall of positive items compared to negative items across all stimulation conditions. However, there were no significant two-way tDCS × valence interactions for reaction times ($F_{(2,55)} = .132, p = .877$) and recall ($F_{(2,55)} = .536, p = .588$). Therefore, tDCS did not significantly alter emotional categorization or memory.

**Faces Dot-Probe Tasks (pooled data across durations).** To assess the effect of tDCS, rm-ANOVA was carried out on the vigilance scores with tDCS (unilateral DLPFC, bilateral DLPFC, sham) as a between-subjects variable and emotion (happy, fearful), and stimulus duration (long, short) as within-subjects variables. As expected, there was a significant main effect of emotion ($F_{(1,54)} = 7.406, p = .009$), reflecting positive vigilance scores for fearful faces ($M = 1.70, SD = 26.30$) and negative vigilance scores for happy faces ($M = -12.01, SD = 28.78$). There was also an expected significant main effect of stimulus duration ($F_{(1,54)} = 4.090, p = .048$), indicating that vigilance scores varied at the two different stimulus durations. Although the main effect of tDCS was not significant ($F_{(2,54)} = .152, p = .859$), there was a significant two-way emotion × tDCS interaction ($F_{(2,54)} = 3.191, p = .049$), indicating that emotional vigilance varied depending on the tDCS configuration. The three-way interaction was not significant ($F_{(2,54)} = .483, p = .619$).

**Tolerability and Side Effects**

In general, tDCS was well tolerated, with all participants reporting a mild transient itching/stinging under the electrodes which faded after the first minute of stimulation. One participant requested that the stimulation be terminated after 5-10 seconds of because of discomfort from the itching/stinging sensation under the electrodes. After the device was switched off, there was no lasting discomfort from this participant. No other adverse effects were reported.
Supplemental References


