

Maria Ironside

**Title page:**

**Frontal cortex stimulation reduces vigilance to threat: implications for the treatment of depression and anxiety**

Ms Maria Ironside<sup>a</sup>, Dr. Jacinta O’Shea<sup>b</sup>, Prof. Philip J Cowen<sup>a</sup> and Prof. Catherine J Harmer<sup>a</sup>

<sup>a</sup> Department of Psychiatry, University of Oxford

<sup>b</sup> Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB), Nuffield Department of Clinical Neurosciences, University of Oxford

Address correspondence to Maria Ironside, University of Oxford, Dept. Psychiatry, Warneford Hospital, Headington, OX3 7JX, [maria.ironside@psych.ox.ac.uk](mailto:maria.ironside@psych.ox.ac.uk)

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## **Abstract:**

### **Background:**

The difficulty in treating mood disorders has brought about clinical interest in alternative treatments, such as transcranial direct current stimulation (tDCS) of the dorsolateral prefrontal cortex (DLPFC). However, the optimal parameters for stimulation and underlying mechanisms of action are unclear. Psychiatric treatments have acute effects on emotional processing which predict later therapeutic action. Such effects have been proposed as cognitive biomarkers for screening novel treatments for depression and anxiety.

### **Methods:**

This study assessed the effect of tDCS on a battery of emotional processing measures sensitive to antidepressant/anxiolytic action. To refine optimal stimulation parameters, DLPFC stimulation using two common electrode montages was compared to sham. 60 healthy volunteers received 20 minutes of active or sham DLPFC stimulation, before completing computerised emotional processing tasks, including a dot-probe measure of vigilance to threat.

### **Results:**

Relative to sham stimulation, participants receiving simultaneous anodal stimulation of left DLPFC and cathodal stimulation of right DLPFC (bipolar-balanced montage) showed reduced vigilance to threatening stimuli. There was no such significant effect when the cathode was placed on the supraorbital ridge (bipolar-unbalanced montage). There were no effects of tDCS on other measures of emotional processing.

## **Conclusions:**

Our findings provide the first experimental evidence that modulating activity in the DLPFC reduces vigilance to threatening stimuli. This significant reduction in fear vigilance is similar to that seen with anxiolytic treatments in the same cognitive paradigm. The finding that DLPFC tDCS acutely alters the processing of threatening information suggests a potential cognitive mechanism that could underwrite treatment effects in clinical populations.

## **Key words:**

Non-invasive brain stimulation, tDCS, depression, anxiety, cognitive biases, emotional processing

## **Text:**

### **Introduction:**

The difficulty in treating mood and anxiety disorders [1] has raised clinical interest in alternative treatments, such as transcranial direct current stimulation (tDCS) of the dorsolateral prefrontal cortex (DLPFC) [2]. TDCS is a neuromodulatory technique that uses weak electrical current to modify the probability of spontaneous neural activity in the stimulated brain region, by acutely increasing or decreasing resting membrane potential [3]. Induced changes in tissue excitability can persist over minutes to hours after stimulation, effects that are NMDA receptor-dependant, and are presumed to reflect changes in synaptic efficacy and plasticity [4-7]. Another form of non-invasive brain stimulation, repetitive transcranial magnetic stimulation (rTMS) applied to the left DLPFC has been approved by the US Food and Drug Administration (FDA) for the treatment of depression since 2008 and is clinically available in the US and Canada [8, 9]. However, tDCS is better tolerated than TMS and is cheaper and simpler to administer, with the development of home use devices potentially broadening clinical research. A number of recent studies have indicated that repeated administration of prefrontal tDCS may be an effective treatment for depression [10-12]. One recent clinical trial in a sample of 120 depressed patients [12] compared repeated treatment with DLPFC tDCS to treatment with the antidepressant drug sertraline (50 mg/d). The results suggested that the combined effects of tDCS and sertraline relieved depressive symptoms more quickly and to a greater extent than either treatment alone. In addition tDCS showed a similar level of efficacy to sertraline, but only tDCS (and not sertraline) was superior to placebo in this trial. These results highlight the potential value of tDCS in the treatment of mood disorders such as depression and anxiety.

However, the optimal parameters for stimulation in the treatment of depression have not been established and there is still uncertainty about the underlying mechanisms of action. Two different montages of electrode placement are most commonly used in the depression literature. Both of these montages are bipolar, in that they place both anodal and cathodal electrodes on the head, rather than having an extracephalic reference electrode. Both montages place the anodal electrode over the left

DLPFC (F3 in the 10/20 system of electrode placement) but differ in where the cathodal electrode is placed. In line with recommended tDCS montage naming conventions [13], we refer to these two montages as 'bipolar-balanced' [12, 14], in which the cathode is placed over the right DLPFC, and 'bipolar-unbalanced' [10] [11], in which the cathode is placed over the right supraorbital ridge, a frequently used reference location in tDCS studies to minimise local cortical excitation [15]. Effect sizes in the treatment of depression vary across studies and there is no consistent pattern of efficacy as a function of electrode montage, though this is difficult to assess fully, given multiple differences in procedures across studies (such as current strength and number of sessions). The current study therefore directly assessed the effects of each of these two DLPFC stimulation montages (bipolar-balanced and bipolar-unbalanced) in changing emotional processing compared to normal (sham tDCS condition), using an experimental medicine model relevant to depression and anxiety.

The cognitive neuropsychological model of antidepressant drug action suggests that treatments for depression and anxiety work by reversing negative affective biases in information processing [16]. Depressed and anxious patients typically show negative biases in perception and memory, and such biases in emotional processing are believed to play a fundamental role in the maintenance of mood disorders [17]. Following the administration of anxiolytic and antidepressant treatment, early changes in emotional processing have been observed in healthy people [18] and clinical groups [19], in the absence of acute subjective mood improvements. These early changes in emotional processing are predictive of later therapeutic response [20, 21]. Acute behavioural measurements can be designed to selectively probe distinct domains of altered cognition characteristic of different mood disorders, such as vigilance to threat observed at short stimulus durations in anxiety disorders [21] versus more effortful interpretive cognition at longer stimulus durations which is known to be affected by depressive symptoms [22]. This is because different stimulus characteristics are relevant to the cognitive schemata that underlie distinct (albeit partially overlapping) disorders [23], such as threat in anxiety versus sadness in depression [24]. Dot-probe studies in distinct clinical groups, in which short and long duration trials have been interleaved within a single test session, have demonstrated this dissociation of negative biases at short durations in anxiety versus at longer

stimulus durations in depression [25, 26]. Hence, to test whether tDCS would induce more of an anxiolytic-like versus anti-depressant type effect, we used a similar measurement approach in the present study. Hence, acute positive shifts in emotional processing induced by an intervention (e.g.: tDCS) may provide a cognitive biomarker for understanding and screening different treatments for depression and anxiety, and allow optimal dosage parameters to be determined prior to a full scale randomised controlled trial.

Depression has been associated with over-activity of limbic areas, such as the amygdala, in response to negative stimuli, coupled with deficient regulation of these responses by higher order areas including the DLPFC [27, 28]. Such processes are believed to contribute to the increased salience of, and behavioural response to negative information in depression. The application of tDCS over the DLPFC in depression has been suggested to work by increasing pre-frontal regulation of limbic responses to negative stimuli [29]. We hypothesised that if tDCS increases prefrontal regulation during negative emotional processing, then this would predict reduced attention and/or memory for negative versus positive emotional material after stimulation. In addition, attentional control is highlighted in models of trait anxiety [30] and DLPFC activity has been negatively correlated with trait anxiety in neuroimaging studies examining attentional control over emotional [31] and non-emotional [32] stimuli. This suggests that modulating DLPFC activity has the potential to causally modify attentional control which has particular relevance to trait anxiety.

Emotional processing has not been extensively examined in brain stimulation research to date. TMS over the medial frontal cortex was shown to impair the processing of angry facial expressions in healthy volunteers [33]. A recent study in healthy volunteers indicated that attentional bias modification training (ABM), involving training attention away from threatening stimuli, can be enhanced when it is paired with tDCS (1mA, 17 min, monopolar left) to the DLPFC [34], indicating a causal role for DLPFC activity in the development of attentional control relevant to anxiety. However, in the literature with clinical groups, tDCS in depression has always and only been applied while patients were at rest (for a review, see [2]). Therefore, to maximize relevance of the current

study to the existing literature describing efficacy in these clinical groups, we examined the acute effects of tDCS applied while participants were at rest. The most comparable previous study in the literature involved a single session of tDCS (1mA, 10 min, bipolar-unbalanced DLPFC) in healthy participants, which speeded reaction times to positive and negative emotional faces [35]. Another study with a depressed group showed a single session of tDCS (2mA, 20 min, bipolar-balanced DLPFC) improved cognitive control for positive relative to negative words in an emotional Stroop task compared to sham stimulation [29]. Although promising, both of these studies used tasks not previously validated for prediction of psychiatric treatment response and therefore these results do not directly indicate potential treatment efficacy. The current phase-I, experimental medicine model study therefore assessed the effects of a single 20 minute session of bipolar-balanced and bipolar-unbalanced tDCS to the DLPFC compared to sham stimulation, in a sample of healthy volunteers, using a battery of cognitive measures previously validated to detect early effects of antidepressant and anxiolytic treatment in both healthy volunteers and in psychiatric patient groups.

## **Methods and Materials:**

### **Participants:**

Ethical approval was obtained from the University of Oxford Central University Ethics Committee (MSD-IDREC-C1-2013-03CUREC). 60 healthy participants (aged 18-45, 30 female) were recruited using print and online advertisements; they were reimbursed for their time and travel expenses at a rate of £10 per hour (see Supplemental Information for more details).

### **Design:**

This study used a between-groups double-blind design with three groups of 20 participants randomised to each condition (active bipolar-balanced DLPFC tDCS, active bipolar-unbalanced DLPFC tDCS, or sham tDCS - which condition was randomized across both active stimulation montages). On the day of the study participants filled out some mood questionnaires before receiving

tDCS while they sat at rest. After the stimulation ended the questionnaires were repeated and then participants carried out a series of computerised emotional processing tasks (details of questionnaires and tasks below).

### **Transcranial Direct Current Stimulation (tDCS):**

Stimulation was delivered using a battery powered device (DC Stimulator Plus, Neuroconn, Germany [36]). The rubber electrodes (25cm<sup>2</sup>) were placed in saline soaked sponges and affixed to the scalp with a rubber band. The two active conditions differed in the electrode montage used. The bipolar-balanced active condition had the anode (positive) electrode on the left DLPFC and the cathode (negative) electrode on the right DLPFC (F3 and F4 respectively, in the 10/20 system of electrode placement). The bipolar-unbalanced active condition had the same anode placement but the cathode was placed on the supraorbital ridge (F8 in the 10/20 system). Stimulation (20 minutes at 2mA) was applied while the participant sat at rest. See Supplemental Information for details of sham and blinding.

### **Mood questionnaire measures:**

See Supplemental Information.

### **Behavioural measures:**

The behavioural tasks were carried out in a predetermined order (Fig.1).

Recognition of facial expression, emotional categorisation and memory were assessed as previously described [37] (see Supplemental Information).

To assess vigilance to threat, participants were presented with a series of image pairs (faces) on a computer screen and asked to respond as quickly and as accurately as possible when they saw a probe (two dots in two different orientations) appear behind one of the image pairs (192 pairs over 10-15 min). Dot-probe task stimuli were fully counterbalanced for emotional face location (top vs.

bottom), dot pair orientation (horizontal versus vertical) and stimulus-response button press mapping (left/right). Two different stimulus durations were used (100 or 1000 ms, (in separate blocks) in order to probe distinct cognitive biases. This task was programmed in E-prime stimulus presentation software (E-prime 1.2, Psychology Software Tools, USA[38]) and was completed 20-25 minutes after the tDCS stimulation ended.

There were three different possible face stimuli pairs: happy-neutral, fearful-neutral, and neutral-neutral. The dot-probe task typically uses either or fearful faces as the negative emotional stimulus. It has been shown, using simultaneous measures of reaction time and eye movements during dot-probe performance, that vigilance scores do not differ regardless of which face type is used [39]. However, neuroimaging research typically indicates that the amygdala is more reactive to fearful than angry faces [40, 41]. For this reason, much recent dot-probe research has used fearful faces [42, 43], as in the present study.

‘Emotional vigilance’ was operationally defined as the difference in reaction time to the probe when it was located behind the emotional face (happy/fearful) of a pair versus when the probe was located behind the neutral face of the same type of pair. Thus, the probe measures the degree of attentional allocation to the emotional faces relative to the neutral faces. Increased vigilance to threat (positive values) is indicated by faster reaction times when the probe is behind the fearful face versus the neutral face (in neutral-fearful pairs). Reduced vigilance (negative values) is indicated by slower reaction times (e.g. when the probe is behind the happy face versus the neutral face in neutral-happy pairs). When the reaction times for emotional and non-emotional faces are the same or very similar, there is no vigilance. The faces dot-probe task interleaved an equal number of blocks of long and short trials, where the faces were shown for two different durations before the probe (100ms and 1000ms). These two different durations were both tested because each duration is thought to measure different types of emotional processing (fast versus slow) relevant to different clinical disorders (anxiety versus depression) [44].

Accuracy and reaction times were recorded for all tasks. Please see Supplemental Information for Calculations and Statistics.

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Insert Figure 1 about here

## **Results:**

### **Group matching:**

The groups did not differ in terms of gender, age, highest education level, personality profile and baseline mood questionnaire measures (see Table 1 and Supplemental Information).

### **Questionnaire based measurements:**

Stimulation did not significantly affect the mood questionnaire measures (see Table 1 and Supplemental Information).

### **Behavioural measurements:**

TDCS did not significantly alter facial expression recognition, emotional categorisation or emotional memory (see Supplemental Information).

**Faces Dot-Probe Tasks:** ‘Emotional vigilance’ was operationally defined as the difference in reaction time to the probe when it was located behind the emotional face (happy/fearful) of a pair versus when the probe was located behind the neutral face of the same type of pair, with positive scores representing greater vigilance (faster reaction times) for the emotional face compared to the neutral face and negative scores representing less vigilance (slower reaction times) for the emotional face compared to the neutral face. Face pairs were presented at two different durations, short (100ms) and long (1000ms), which were analysed independently. Analysis of short-duration trials aimed to test whether tDCS would abolish fear vigilance that is characteristic of rapid responses to threat seen in anxiety disorders. Analysis of long-duration trials tested whether tDCS would abolish fear

vigilance on a slower timescale that is characteristic of the more effortful, negative interpretative cognition seen in depression.

**Short duration dot-probe task (100ms):** Before testing for a change in behaviour with tDCS, we first examined whether the expected fear vigilance phenomenon was present at baseline. Paired samples t-tests were carried out on the reaction times in the sham condition, for fearful/neutral face pairs. Participants exhibited the expected pattern of significant fear vigilance (faster reaction times when the probe was located behind the fearful face versus the neutral face of a pair) ( $t(18) = 3.569$ ,  $p = .002$ ; mean paired differences = 27.47,  $SD = 33.55$ ) (Fig. 2).

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Insert Figure 2 about here

To assess the effects of tDCS on the baseline (sham) pattern of emotional vigilance, rm-ANOVA was carried out on the vigilance scores with tDCS (active bipolar-balanced, active bipolar-unbalanced, sham) as a between-subjects variable, and emotion (happy, fearful) as a within-subjects variable. As expected, there was a significant main effect of emotion ( $F(1, 54) = 7.494$ ,  $p = .008$ ), reflecting overall positive vigilance scores for fearful faces ( $M = 10.65$ ,  $SD = 38.95$ ) and negative vigilance scores for happy faces ( $M = -9.46$ ,  $SD = 34.822$ ). Although the main effect of tDCS was not significant ( $F(2, 54) = .857$ ,  $p = .430$ ), there was a significant two-way emotion  $\times$  tDCS interaction ( $F(2, 54) = 3.251$ ,  $p = .046$ ), suggesting that the baseline pattern of emotional vigilance was altered significantly, in a manner that depended on the tDCS configuration.

To clarify the nature of the tDCS-induced change in emotional vigilance, two separate one-way ANOVAs were conducted on vigilance scores for each emotion. For vigilance to happy faces there was no effect of tDCS ( $F(2, 54) = .890$ ,  $p = .417$ ), but for vigilance to fearful faces there was a significant effect of tDCS ( $F(2, 54) = 3.594$ ,  $p = .034$ ). Planned contrasts against the sham condition revealed that this significant between-groups effect was driven by a significant reduction in fear

vigilance in the active bipolar-balanced tDCS condition compared to sham ( $t(54) = 2.679$ ,  $p = .005$ ; active bipolar-balanced:  $M = -4.55$ ,  $SD = 39.81$ ; sham:  $M = 27.42$ ,  $SD = 33.65$ ). Whereas participants in the sham tDCS condition exhibited the expected pattern of greater vigilance towards fearful and reduced vigilance towards happy faces, this was abolished by active bipolar-balanced tDCS (Fig. 3). 1-sample t-tests (1-tailed, against zero) on the vigilance scores confirmed that participants in the active bipolar-balanced condition neither showed significantly greater vigilance towards fearful faces ( $t(19) = -.511$ ,  $p = .308$ ), nor significantly less vigilance towards happy faces ( $t(19) = -.153$ ,  $p = .440$ ), by contrast with the sham condition (fearful faces:  $t(18) = 3.552$ ,  $p = .001$ , happy faces:  $t(18) = -1.960$ ,  $p = .033$ ). Hence, participants in the bipolar-balanced tDCS condition showed similar vigilance towards fearful, happy and neutral face stimuli. Although the active bipolar-unbalanced tDCS condition showed a similar numerical trend (reduction in fear vigilance), this did not quite reach statistical significance ( $t(54) = -1.435$ ,  $p = .079$ ). Direct contrast of the two active tDCS conditions was also not significant ( $t(54) = 1.188$ ,  $p = .240$ ), and the observed pattern of data (intermediate between the sham and bipolar-balanced conditions, (Fig. 3) suggests that bipolar-unbalanced tDCS had only a partial attenuating effect. Hence, only bipolar-balanced tDCS significantly abolished the normal pattern of fear vigilance. A one-way ANOVA revealed no effect of tDCS on accuracy in this task ( $F(2, 52) = .818$ ,  $p = .447$ ).

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Insert Figure 3 about here

**Long duration dot-probe task (1000ms):** Before testing for a change in behaviour with tDCS, we first examined whether the expected fear vigilance phenomenon was present at baseline. Paired samples t-tests were carried out on the reaction times in the sham condition for fearful/neutral face pairs. There was no evidence of fear vigilance ( $t(18) = -.759$ ,  $p = .458$ ; mean paired differences = 7.95,  $SD = 45.63$ ) (Fig. 2). Given that the absence of measurable fear vigilance at baseline, there was no behavioural phenomenon present for tDCS to change. Hence, the long duration trials were not analysed further for effects of tDCS. A one-way ANOVA revealed no effect of tDCS on accuracy in this task ( $F(2, 52) = 2.221$ ,  $p = .119$ ).

See Supplemental Information for data on tolerability and adverse effects.

## **Discussion**

These findings provide the first experimental evidence that modulating activity in the dorsolateral prefrontal cortex leads to reduced vigilance to threatening stimuli. This study is also the first to directly compare the two most common electrode montages used for DLPFC tDCS, with the results favouring the bipolar-balanced montage. In this study, the group receiving sham stimulation displayed the expected attentional bias towards fearful faces on short stimulus duration trials. Healthy participants typically show this pattern of increased vigilance (faster reaction times) for fearful faces compared to neutral faces, an effect known to be attenuated by anti-depressant and anxiolytic treatment [45]. This negative bias (i.e. increased vigilance to threat) was reversed with tDCS of the DLPFC. One of the key aims of this study was to test two DLPFC stimulation electrode montages commonly used in clinical research. The bipolar-balanced montage significantly abolished the normal pattern of fear vigilance observed in the sham condition. By contrast, although a similar numerical trend was observed in the bipolar-unbalanced condition (Fig. 3), this did not reach significance. This suggests a partial effect, likely reflecting the fact that both electrode montages involve anodal stimulation of left DLPFC. The fact that only the bipolar-balanced condition significantly changed fear vigilance from normal (sham) suggests that intervening bilaterally, to change activity in both left and right DLPFC, may be critical for the anxiolytic-like effect we observed. These results highlight a role for stimulation of the DLPFC in modulating attentional bias to threat.

Attentional bias to threat, particularly at short exposure durations, has been particularly associated with anxiety disorders [46]. Indeed, volunteers high in trait anxiety or with DSM anxiety disorders typically show enhanced vigilance to threatening face or word cues at short durations [47]. Consistent with this, anxiolytic interventions reduce bias towards threat in this paradigm, an effect also seen in healthy volunteers. In particular, the administration of the SSRI citalopram [45] and the

benzodiazepine diazepam [48] were found to reduce fear vigilance in healthy volunteers using a similar dot-probe task. A parallel study using an exposure-based cognitive behavioural intervention for panic disorder also revealed an early effect of treatment on vigilance to fearful faces and this effect predicted subsequent reduction in anxiety following treatment [21]. Together, these results suggest that tDCS has an anxiolytic-like profile in this task, and that these effects can be seen most clearly with bipolar-balanced DLPFC stimulation. Since a similar pattern of effects on this task has been observed previously both in studies examining the effects of anxiolytic drugs on healthy volunteers and patients undergoing anxiolytic treatment, it is possible that the effects shown in the present study reveal a common mechanism of action for previously reported effects of tDCS on standard measures of mood in clinical trials [12].

TDCS did not lead to a widespread change in emotional processing across the other measures used in this study. Whereas the other emotional processing tasks in the present study (such as facial expression recognition, emotional categorisation and emotional memory) are typically used to assess antidepressant treatment [22, 49], the dot-probe task is mainly used to measure anxiolytic treatment [48, 50]. The present study suggests that bipolar-balanced DLPFC tDCS reduces vigilance to threat-related emotional stimuli, reminiscent of specific effects seen with anxiolytics like diazepam in this task [48]. Depression and anxiety are the most highly comorbid psychological disorders in primary health care [51] and it can be difficult to separate them in terms of diagnosis and treatment. There is a possibility that the antidepressant effects of tDCS observed in the literature are related to a decrease in anxiety. This is supported by a study which found that during negative imagery visualization, anodal tDCS led to decreased cortisol levels and increased vagal activity, measures which reflect stress regulation [52].

The present phase-I study in healthy volunteers identified an anxiolytic-like profile of tDCS that was specific to the active bipolar-balanced DLPFC stimulation condition. The next logical step is to assess whether the effects reported here in a healthy volunteer experimental medicine model can be found in a patient group, and if they can predict response to treatment of depression and anxiety. The

results from this study support the use of bipolar-balanced DLPFC stimulation paradigms and measurements of attentional bias. These measurements have been identified as a marker of efficacy in other treatments and so this protocol could have a similar effect in a clinical population, where reductions in negative biases have been shown to predict later clinical improvement [19, 21]. The focus of this study was to investigate acute effects of tDCS, by testing for an induced change in emotional processing similar to what has previously been observed acutely with antidepressant or anxiolytic treatment. However, it will also be necessary to evaluate whether these effects seen acutely can be extended over time with repeated interventions, as occurs with antidepressant drug treatment.

The present study suggests that modulating DLPFC activity can change attentional bias (fear vigilance at short stimulus durations) that is relevant to clinical anxiety [53]. Brain imaging studies have revealed hypo-activation of the DLPFC in anxiety [30-32], which is thought to reflect deficient attentional control [54]. The present study suggests a causal relationship between DLPFC stimulation and attention to threat, since changing DLPFC activity abolished fear vigilance. Future studies, by combining tDCS with fMRI, could cast light on the functional brain changes that mediate this effect. For instance, reduced DLPFC activity is thought to cause reduced top down inhibitory control over limbic regions, which are hyper-activated in response to negative emotional stimuli in anxiety [28]. We are currently testing this hypothesis that tDCS alters prefrontal-limbic functional interactions during emotional processing. In addition, further studies exploring the cognitive sub-components of vigilance to threat (e.g. difficulty to disengage, see [55]) could provide additional insights into the specific nature of the tDCS effect.

Since the dot-probe task was conducted ~22 minutes after the end of stimulation, it is conceivable that, in some individuals, the physiological after-effect of tDCS may have already decayed by that time. The duration of after-effects of frontal tDCS has not been studied systematically. However, in motor cortex, the same stimulation protocol used here (2mA, 20 minutes) changed cortical excitability with effects lasting for at least 90 minutes after stimulation

offset [56]. In our study, the dot-probe tasks were carried out ~22-37 min after stimulation. Hence, testing was conducted reliably within the likely time window of tDCS after-effect.

The current phase-I results in healthy volunteers reveal an anxiolytic-like effect of dorsolateral prefrontal cortex tDCS on a cognitive biomarker relevant to clinical anxiety, and indicate a potential neurocognitive mechanism (reduced fear vigilance) that may partially mediate the reported findings of clinical efficacy of prefrontal tDCS in the literature. In this first direct comparison of two electrode montages used in the depression literature, the data indicate preferential use of a bipolar-balanced rather than bipolar-unbalanced DLPFC stimulation montage.

In summary, this study offers an experimental medicine framework and a sensitive cognitive biomarker that could be used for future testing, refining and validating the novel intervention of prefrontal tDCS to mitigate anxiety and depression. By contrast with the more empirical approach to devising tDCS interventions that characterizes the existing literature (as reflected in the great heterogeneity of stimulation parameters), here we outline a principled approach, and describe an anxiolytic-like stimulation profile on a laboratory test of proven clinical predictive utility. Hence, the value of our study is that it offers a principled path towards testing and benchmarking novel stimulation protocols at the development phase, either in healthy volunteers or in clinical populations, in order to optimize treatment efficacy for depression and anxiety.

Maria Ironside

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Maria Ironside

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## **Tables/Figure Legends:**

**Figure 1: Timeline of tDCS and behavioural tasks.** Values above the arrow denote time elapsed after tDCS (min), values below the arrow denote task duration (min).

**Figure 2: Significant fear vigilance was present in the short duration dot-probe task (100ms) but not in the long duration dot-probe task (1000ms).** Mean reaction times (ms) when the probe was located behind the fearful face of a fearful/neutral pair versus when the probe was located behind the neutral face of a fearful/neutral pair. Asterisks (\*\*) denote a significant decrease in reaction times for fearful faces compared to neutral faces ( $p = .001$ ). Error bars represent  $\pm 1$  standard error of the mean.

**Figure 3: Dot-probe emotional vigilance.** Vigilance scores represent the difference between reaction times (ms) when the probe was located behind the emotional face versus when the probe was located behind the neutral face of the same pair type. In the sham condition, participants exhibited the expected normal pattern of increased vigilance to threat (positive values on y axis), and reduced vigilance to happy faces (negative values on y axis). Bipolar-unbalanced stimulation of prefrontal cortex did not significantly alter this pattern, but bipolar-balanced stimulation abolished it. Asterisks (\*\*) denote a significant decrease in fear vigilance in the bipolar-balanced tDCS condition compared to sham stimulation ( $p = .005$ ). Error bars represent  $\pm 1$  standard error of the mean.

**Table 1: Group statistics**

Variable	Group means (+ SD)			Test statistics
	Sham	Bipolar- unbalanced	Bipolar- balanced	
Age	25.95 (6.63)	24.50 (4.04)	23.55 (3.99)	$F(2,57) = 1.149, p=.324$
Education level <sup>a</sup>	3.45 (.759)	3.45 (.686)	3.1 (.912)	$F(2,57) = 1.304, p=.279$
EPQ <sup>b</sup> – Neuroticism	4.20 (4.03)	5.10 (3.46)	5.60 (3.69)	$F(2,57) = .721, p=.491$
EPQ <sup>b</sup> – Psychoticism	3.45 (1.93)	3.05 (2.50)	2.75 (2.22)	$F(2,57) = .496, p=.612$
EPQ <sup>b</sup> – Lie	9.70 (5.06)	8.95 (3.90)	8.15 (3.76)	$F(2,57) = .656, p=.523$
EPQ <sup>b</sup> – Extraversion	13.5 (5.09)	16.2 (4.11)	14.5 (3.97)	$F(2,57) = 2.085, p=.134$
Baseline BDI <sup>c</sup>	1.95 (2.82)	1.4 (2.21)	1.8 (2.59)	$F(2,57) = .235, p=.792$
Change VAS <sup>d</sup> happy	+.45 (1.39)	+.05 (.62)	+.1 (.97)	$F(2,56) = .845, p=.435$
Change VAS <sup>d</sup> sad	-.05 (.76)	-.11 (.46)	-.15 (.48)	$F(2,56) = .146, p=.865$
Change VAS <sup>d</sup> hostile	+.15 (.67)	-.05 (.41)	+.05 (.22)	$F(2,56) = .900, p=.412$
Change VAS <sup>d</sup> alert	0 (1.62)	-.53 (1.31)	-.15 (1.27)	$F(2,56) = .717, p=.493$
Change VAS <sup>d</sup> anxious	-.30 (1.89)	-1.00 (1.63)	-.55 (1.05)	$F(2,56) = .997, p=.375$
Change VAS <sup>d</sup> calm	+.8 (2.24)	+.11 (2.81)	-.25 (1.41)	$F(2,56) = 1.161, p=.320$
Change PANAS <sup>e</sup> positive	+.37 (4.44)	-.95 (4.79)	-.2 (3.81)	$F(2,56) = .449, p=.640$
Change PANAS <sup>e</sup> negative	-.32 (3.90)	-.45 (1.82)	-1.0 (1.8)	$F(2,56) = .364, p=.697$

**Table 1: Group statistics:**

Group statistics for baseline measures and change scores on mood ratings (post tDCS - pre tDCS).

<sup>a</sup> Educational ratings: 1= GCSE, 2= A-level, 3= Undergraduate degree, 4= Postgraduate degree

<sup>b</sup> EPQ: Baseline Eysenck personality questionnaire scores

<sup>c</sup> BDI: Baseline Beck Depression Inventory scores

<sup>d</sup> VAS: Visual Analogue Scale change scores (post tDCS - pre tDCS)

<sup>e</sup> PANAS: Positive and Negative Affective Schedules change scores (post tDCS - pre tDCS)