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Prefrontal cortex stimulation does not affect emotional bias, but may slow emotion identification

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Abstract

Transcranial direct current stimulation (tDCS) has recently garnered attention as a putative depression treatment. However, the cognitive mechanisms by which it exerts an antidepressant effect are unclear: tDCS may directly alter 'hot' emotional processing biases, or alleviate depression through changes in 'cold' (non-emotional) cognitive function. Here, 75 healthy participants performed a facial emotion identification task during 20 minutes of anodal or sham tDCS over the left dorsolateral prefrontal cortex (DLPFC) in a double-blind, within-subject crossover design. A subset of 31 participants additionally completed a task measuring attentional distraction during stimulation. Compared to sham stimulation, anodal tDCS of the left DLPFC resulted in an increase in response latency across all emotional conditions. Bayesian analysis showed definitively that tDCS exerted no emotion-dependent effect on behaviour. Thus, we demonstrate that anodal tDCS produces a general, rather than an emotion-specific, effect. We also report a preliminary finding in the subset of participants who completed the distractibility task: increased distractibility during active stimulation correlated significantly with the degree to which tDCS slowed emotion identification. Our results provide insight into the possible mechanisms by which DLPFC tDCS may treat symptoms of depression, suggesting that it may not alter emotional biases, but instead may affect 'cold' cognitive processes.

Key words: distractibility; depression; DLPFC; tDCS

Introduction

Over the past decade a form of noninvasive brain stimulation, anodal transcranial direct current stimulation (tDCS), has been reported to be effective in treating depression, both alone (Fregni *et al.*, 2006; Boggio *et al.*, 2008; Loo *et al.*, 2012) and in combination with antidepressant medication (Brunoni *et al.*, 2013). Anodal tDCS delivers a weak electric current that modulates cortical excitability, although the precise mechanisms underlying its effects are largely unknown.

Anodal tDCS has been used to directly target one of the most reliably identified neural correlates of depression, dysfunction of the dorsolateral prefrontal cortex (DLPFC) (Koenigs and Grafman, 2009). During the resting state, metabolism in the DLPFC has been found to be reduced in depression (Baxter *et al.*, 1989, Biver *et al.*, 1994, Galynker *et al.*, 1998); by contrast, task-related functional magnetic resonance imaging (fMRI) studies consistently show exaggerated DLPFC activation, particularly during more challenging cognitive tasks (Wang *et al.*, 2015). Targeting the DLPFC with tDCS therefore aims to remedy the activity-dependent 'cortical inefficiency' hypothesised to occur in this region (Nord and Roiser, 2015), with possible downstream effects on dysregulation in other circuits driving biased emotional processing (Roiser *et al.*, 2012). However, despite

preliminary findings of antidepressant efficacy (Shiozawa *et al.*, 2014), there is a dearth of research on the cognitive mechanisms that may drive the beneficial effects of DLPFC tDCS.

Hot and cold cognition in depression

Among the neural systems implicated in the neurobiology of depression, two networks are thought to play a particularly important role, and have been targeted in the context of novel treatments for depression. The first system is implicated in emotion and reward processing, often termed 'hot' cognition, and includes limbic structures as well as the ventral prefrontal cortex, in particular the subgenual anterior cingulate cortex (Drevets *et al.*, 2008). Disruptions in this system are thought to drive the characteristic depressive bias in 'hot' cognition, away from positive and towards negative information processing (Bradley and Mathews, 1983). The second system is associated particularly with effortful 'cold' (non-emotional) cognitive processing, and includes the dorsal anterior cingulate cortex, the hippocampus, and the DLPFC (Roiser and Sahakian, 2013).

If the mechanism driving any antidepressant effects of DLPFC stimulation were similar to that of traditional pharmacological treatments, there might occur an acute effect of tDCS on hot cognition in depression. Although the therapeutic effect of antidepressant drugs typically takes 4-6 weeks, acute doses have been shown to produce positive emotional biases, in both healthy controls (Harmer *et al.*, 2003) and depressed patients (Harmer *et al.*, 2009a). These effects are thought to elicit downstream changes, through the relearning of internal models of the environment (schemata), ultimately resulting in symptom remission (Harmer *et al.*, 2009b).

Despite the central importance of hot processing in contemporary theories of depression, this area has been almost entirely neglected in tDCS research, with a small number of exceptions. In one study, DLPFC tDCS did not elicit subjective emotional changes, but subtly improved identification of positive emotional expressions in healthy subjects (Nitsche *et al.*, 2012); in another, DLPFC tDCS decreased vigilance to threatening stimuli (Ironside *et al.*, 2015), a result akin to the effect of anxiolytic drugs such as diazepam (Murphy *et al.*, 2008). However, in the latter study, tDCS did not affect any other measures of emotional processing in a comprehensive battery of tasks (Ironside *et al.*, 2015).

Another possibility is that DLPFC tDCS exerts an antidepressant effect through mechanisms altogether distinct from those involved in antidepressant drug treatment. Instead, tDCS might only directly affect cold cognitive processing in depression, but this could potentially catalyse the changes in emotional processing that are thought to drive the remission of symptoms (Roiser *et al.*, 2012). Disruptions in cold cognition in depression, which are part of standard diagnostic criteria, typically manifest as impairments in attention, cognitive control, and working memory, and have been hypothesised to be caused by inefficiency in regions such as the DLPFC (Harvey *et al.*, 2005). There is evidence that anodal DLPFC tDCS improves working memory (Andrews *et al.*, 2011, Lally *et al.*, 2013) and cognitive control (Vanderhasselt *et al.*, 2013). However, there is also evidence that anodal DLPFC tDCS increases self-reported mind-wandering, as measured using subjective reports of task-unrelated thoughts (e.g., 'what shall I eat for lunch today?'; versus a task-related thought such as 'what is the correct button to press now?'). This is of particular relevance to depression, as a central symptom of depression, rumination, involves fixation on negative thoughts. Depressive thinking is associated with mind-wandering

(Smallwood *et al.*, 2007), but mind-wandering itself does not decrease mood (Poerio *et al.*, 2013). Instead, distraction has been shown to alleviate depressed mood, potentially through alleviation of rumination (Nolen-Hoeksema and Morrow, 1993). If tDCS does indeed increase mind-wandering (Axelrod *et al.*, 2015, Kajimura and Nomura, 2015), this could provide a second possible mechanism for its antidepressant effects: an increase in distractibility.

Drawing on the consistent reports of emotional processing biases in depression, and the evidence that standard antidepressant drugs normalize these, the main aim of this study was to test whether DLPFC tDCS positively biases emotional processing. We used a well-validated task involving the identification of morphed emotional expressions. We hypothesized that if anodal left DLPFC tDCS exerts antidepressant effects through modulating hot cognition, it should elicit a positive bias in emotional face identification, similar to the acute effects of antidepressant drugs. In a subgroup of participants, we also tested a specific hypothesis that tDCS might affect distractibility. To this end, we employed an experimental paradigm that measures the effect of irrelevant distractors on attentional performance (Forster and Lavie, 2008), which has been shown to correlate with internal distraction from mind-wandering (Forster and Lavie, 2014), allowing us to use this as an index of individual variability in distractibility.

Materials and methods

Participants and procedure

Seventy-five healthy participants (40 females; mean age 25.6) were recruited via the online University College London Psychology Subject Pool. Exclusion criteria included any history of seizures, and any known neurological or psychiatric disorders, which were assessed by telephone interview prior to the first testing session. All participants gave written informed consent before proceeding with the first day of the experiment, for which they were randomized to either real or sham stimulation, which was delivered while completing the cognitive tasks. Both experimenter and participant were blind to stimulation condition. Participants attended on a second day, at least 24 hours after the first, on which they received the other stimulation type. Participants were compensated for their time and travel, and the study was approved by the NHS Research Ethics Committee for London Queen Square.

Brain stimulation

Anodal transcranial direct current stimulation at 1 mA was generated by a battery-driven stimulator (neuroConn DC-stimulator, Ilmenau, Germany). Sponge coverings were soaked in saline and applied to a pair of 5 x 7 cm electrodes. The anodal electrode was placed over the left DLPFC using the international 10-20 system of electrode placement (Jasper, 1958). The reference electrode was placed on the ipsilateral shoulder deltoid muscle, to ensure that the effects on the brain originated from the anodal stimulation alone (Priori *et al.*, 2008, Wolkenstein and Plewnia, 2013). Anodal and sham stimulation both used an identical electrode montage with the anodal electrode located at F3 in the 10-20 system, and lasted 20 minutes, but anodal stimulation involved a 5-second ramp-up of stimulation after which the current was delivered continuously, whereas sham stimulation delivered a current for only 40 seconds. Participants were randomized using pre-determined codes to allocate sham

versus active stimulation days, with order counterbalanced across participants.

Emotional faces task

The Emotion Recognition Task, programmed in E-Prime, is a six-alternative forced-choice paradigm to measure sensitivity to six emotions (happy, sad, fearful, angry, surprised, and disgusted). Each trial begins with a central fixation cross lasting 1500-2500ms and presents a morphed face stimulus for 150ms, followed by a 250ms noise mask, to prevent afterimages (Bamford *et al.*, 2015). Participants are then required to select the emotion best describing the facial stimulus, using the mouse to click on one of the six emotion types displayed on screen (see Figure 1). The emotion type options appear for 10 000 ms or until the participant responds. Participants completed the task in an average of 6.65 minutes (SD = 1.18).

The 350 × 457 pixel face stimuli were created from photographs of 12 young adults photographed under controlled conditions, and merged into composite images depicting each of the six emotions (Bamford *et al.*, 2015). A face depicting a prototypical expression was also constructed, made up of a composite of 6 emotional and one neutral expression (Bamford *et al.*, 2015). This was so the face would appear genuinely emotionally ambiguous, since recent evidence suggests that emotions are coded with reference to a prototype of this nature (rather than a neutral face) (Skinner and Benton, 2010). A 15-image morph sequence that ran along the continuum from the prototypical face to the full-intensity emotional expression was created for each of the six emotions, with the first image displaying 5% intensity, and the final image displaying 100% intensity. In the task, ninety-six choices were made, sixteen per emotion (half male, half female faces).

One participant experienced inconsistent stimulation on both days due to high electrical impedance which may have occurred due to thick hair (Horvath *et al.*, 2014), and a data saving failure occurred for a second participant (but whose distractibility task data were saved). Both these participants were therefore excluded from all emotion identification data leaving N = 73 in the final analysis.

Distractibility task

In a subset of the participants (N = 31) we administered an attentional distraction task in addition to the emotional faces task, which was also programmed in E-Prime (Forster and Lavie, 2008). For these participants the distractibility task was always administered first during the stimulation session. All stimuli were presented on a laptop screen at a viewing distance of 60cm. Each trial begins with a centrally presented fixation point

presented for 500ms, followed by the stimulus, which consists of a 1.6° radius circle of grey letters ('o') presented on a black background. Participants are instructed to search the stimulus display for a target letter (either X or N, presented for 500ms), for which they make a rapid keyboard response (pressing 0 or 2 for X or N, respectively). Participants complete three slow (1000ms) example trials, and 12 fast (500ms) practice trials, before beginning the full version (480 trials). The task lasted an average of 8.19 minutes (SD = 30.6 seconds). An irrelevant distractor (a cartoon character) is presented in the periphery of the screen, outside the letter circle, on 10% of trials (distractor condition). Participants are directed to respond as quickly and accurately as possible, and to focus only on the letter circle, ignoring any stimulus outside the circle (see Figure 2). Feedback for errors is provided by a brief tone.

The main outcome measure on this task contrasts responses on trials where no distractor was presented with those on which the irrelevant distractor was presented (Forster and Lavie, 2008). In other words, it provides a measure of how distractible a participant is by measuring the degree to which distracting stimuli affect errors and reaction times. This enabled us to test whether (1) anodal tDCS of the DLPFC increased distraction on the task, and (2) whether the effect of tDCS on distraction correlated with any effects of tDCS on emotion identification.

At eight intervals throughout the task, participants were presented with thought probes asking 'What were you thinking about just now?', and instructed to answer whether or not they had experienced task-unrelated thoughts in the trials leading up to the question.

In the thought probes, participants were instructed to report the thought that had been passing through their mind in the moment immediately before the probe appeared. Participants were instructed to press A if they were thinking about the task that they were performing (they were given examples of 'where is the target letter?' and 'oops I've pressed the wrong button'), and to press Z if they were thinking about something unrelated to the task at hand. Participants who pressed Z were then asked whether their thought was positive, negative, or neutral. Very few participants reported positive or negative thoughts, so this measure was not used in any subsequent analyses. Thus, our measure of task-unrelated thoughts reflects only the proportion of probes to which participants reported task-unrelated versus task-related thoughts.

Statistical analysis

For both tasks, differences between the conditions were analysed using Frequentist and Bayesian methods. Frequentist statistical analyses were performed in SPSS 22.0 (IBM Comp,
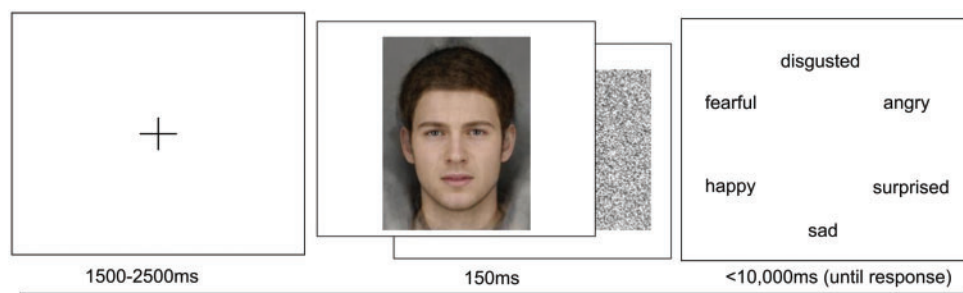

Fig. 1. Structure of the emotion identification task. Each trial begins with a fixation cross, followed by a very brief presentation (150 ms) of an emotional face which is replaced by a mask. Participants responded using the mouse to identify the emotion presented.
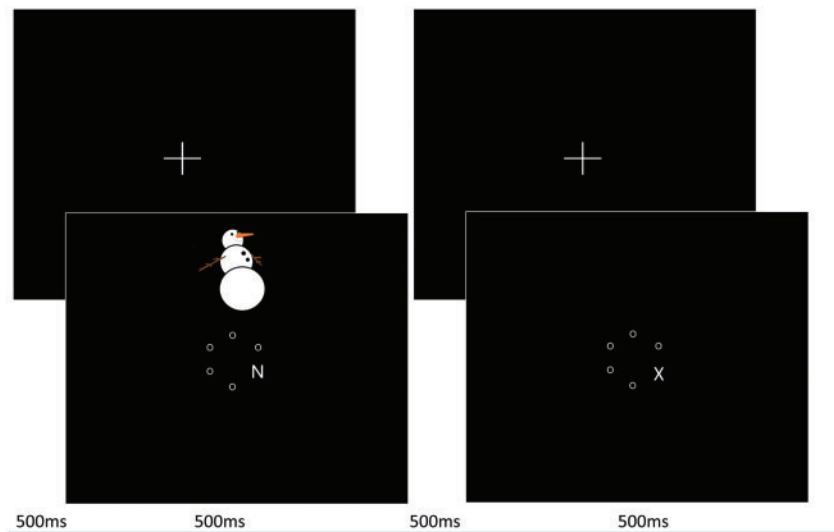
Fig. 2. Structure of the distraction task. Participants are instructed to press 0 for the target letter X, or 2 for the target letter N, as quickly and accurately as possible. The left trial is an example of an irrelevant distractor trial (10% of trials), and the right trial is an example of a typical trial (90% of trials). Note that the specific cartoon shown here is for illustrative purposes only, in order to avoid violating copyright for the images used in the experiment (Spongebob Squarepants, Superman, Spider-Man, Mickey Mouse, Donald Duck, and Pikachu).

Armonk, NY), whilst Bayesian analyses were performed in JASP (version 0.7.5.5), employing the default prior, as in previous reports (Robinson *et al.*, 2015). Both Frequentist and Bayesian repeated-measured analyses of variance (ANOVAs) were constructed to examine how sham or real tDCS affected accuracy and reaction times for each of the six emotion types (for the emotion task) or the two distraction conditions (for the distraction task). We initially included order as a between-subjects factor in all models, and removed it if there was no significant effect of order or any interactions in the Frequentist analyses, or if the model evidence did not support its inclusion in the Bayesian analyses.

Frequentist ANOVAs were used to generate F-statistics and p-values, while Bayesian ANOVAs were used to generate (natural) log Bayes factors ($logBF_{10}$). In JASP, Bayesian ANOVAs are constructed hierarchically, allowing one to calculate the evidence supporting the inclusion of specific factors in the model. In every report of a $logBF_{10}$ statistic, this refers to the evidence for a model containing the relevant main effect(s) (and interactions, where appropriate), relative to a null model. Positive $logBF_{10}$ values indicate evidence in favour of the specified model, while negative values indicate evidence in favour of the null model. Following the convention of Jeffreys (Jeffreys, 1961), we assigned descriptive labels to the magnitudes of (non-log) Bayes factors to aid interpretation: substantial (3–10), strong (10–32), very strong (32-100), and decisive (>100). Where appropriate we additionally report the ratio of Bayes factor scores between models of interest, which can be interpreted as the evidence in favour of one model relative to the other model.

Finally, in the subgroup of participants who completed both tasks, we calculated a measure of the degree to which distractibility (measured by reaction time) was altered by tDCS as:

[distractor condition (real tDCS) – no distractor condition (real tDCS)] –
[distractor condition (sham tDCS) – no distractor condition (sham tDCS)]

We correlated this tDCS-induced distractibility measure with tDCS-induced changes in reaction times on the emotion identification task, using Pearson's correlation coefficients (and the equivalent analysis in JASP).

Power analysis

In the emotion task, with 73 participants, we had >99% power to detect an effect size of $d = 0.5$ at $\alpha = 0.05$ (2-tailed); a recent meta-analysis of anodal DLPFC tDCS for depression reported a mean effect size of $d = 0.49$ (Brunoni *et al.*, 2016). In the distractibility task, with 31 subjects, we had 86% power to detect a true association of $r = 0.5$ at $\alpha = 0.05$ (2-tailed).

Results

Common side-effects of tDCS were recorded for both real and sham tDCS sessions, including itching, burning, and tingling. These effects were no more common under active tDCS than sham stimulation (for a full list of reported side-effects, see Table 1).

Emotion identification task

For the reaction time analysis, there was a significant stimulation-by-order interaction ($F(1,71)=26.39$, $p < 0.001$), representing a practice effect by which participants responded faster on the second testing session, and the evidence for models incorporating the stimulation-by-order interaction was higher than for those without. Therefore order (and where relevant the stimulation-by-order interaction) was retained in both Frequentist and Bayesian reaction time models.

For the accuracy analysis, order of stimulation was removed since no significant interaction between order and stimulation condition was found (Frequentist analyses), and the evidence for models incorporating order was lower than for those without (Bayesian analyses).

Effect of tDCS and emotion on reaction times. The analyses below were performed using reaction time data for correct responses only, but the results were similar when including all responses (data not shown).

Table 1. Side effects reported by participants during real and sham stimulation

% Reporting	Real tDCS (%)	Sham tDCS (%)
Headache	7	7
Neck pain	4	5
Scalp pain	9	9
Tingling	37	35
Itching	37	31
Burning sensation	17	17
Skin redness	9	5
Sleepiness	24	28
Trouble concentrating	17	27
Acute mood change	8	9
Others	1	4

"Others" included abnormal metallic taste (reported during sham), and numbness in the contralateral side of the face (reported during real).

Participants responded significantly more slowly under tDCS ($F(1,71)=6.02$, $p=0.017$), which was confirmed by the Bayesian analysis ($\log BF_{10}=27.20$ for the model including stimulation, order and their interaction).

Reaction times were significantly affected by emotional valence ($F(5,355)=7.4$, $p<0.001$; $\log BF_{10}=7.99$ for the model including emotion and order), with happy, sad, and surprise eliciting shorter reaction times than fear, anger, and disgust (Figure 3a). Paired contrasts revealed that reaction times to angry faces were significantly longer than to happy ($t(72)=3.98$, $p<0.001$), sad ($t(72)=3.29$, $p=0.002$), and surprised faces ($t(72)=5.80$, $p<0.001$), but not fearful ($t(72)=1.29$, $p=0.201$) or disgusted ($t(72)=1.63$, $p=0.108$); while disgusted faces were identified significantly more slowly than happy ($t(72)=2.82$, $p=0.006$) and surprised faces ($t(72)=3.97$, $p<0.001$) (but not fearful ($t(72)=-0.18$, $p=0.862$) or sad ($t(72)=1.35$, $p=0.182$)). Additionally, fearful faces were identified significantly more slowly than happy ($t(72)=2.40$, $p<0.019$) and surprised faces ($t(72)=3.94$, $p<0.001$) (but not sad ($t(72)=1.40$, $p=0.166$)), and sad faces were identified significantly more slowly than surprised faces ($t(72)=2.68$, $p=0.009$).

There was no interaction between stimulation and emotion type on reaction times ($F(5,355)=0.26$, $p=0.93$). Bayesian analysis revealed that the model containing main effects of stimulation, emotion and order, the stimulation-by-emotion interaction, and the stimulation-by-order interaction ($\log BF_{10}=30.90$) scored 266 times (decisively) worse than the winning model ($\log BF_{10}=36.57$), which incorporated only the above main effects and the stimulation-by-order interaction.

Effect of tDCS and emotion on accuracy. We did not find a significant main effect of stimulation on accuracy ($F(1,72)=1.62$, $p=0.21$), which was confirmed by the Bayesian analysis ($\log BF_{10}=-2.37$ for the model only including stimulation, indicating strong evidence in favour of the null).

Accuracy depended significantly on emotion ($F(5,360)=31.95$, $p<0.001$), which was corroborated by the Bayesian analysis ($\log BF_{10}=106.43$ for the model only including emotion, indicating decisive evidence, Figure 3b). Accuracy was higher for identifying happy, sad, and surprised faces, and lower for identifying fearful, angry, and disgusted faces. Paired contrasts revealed that fear was identified significantly less accurately than all other emotions: anger ($t(72)=4.48$, $p<0.001$), disgust
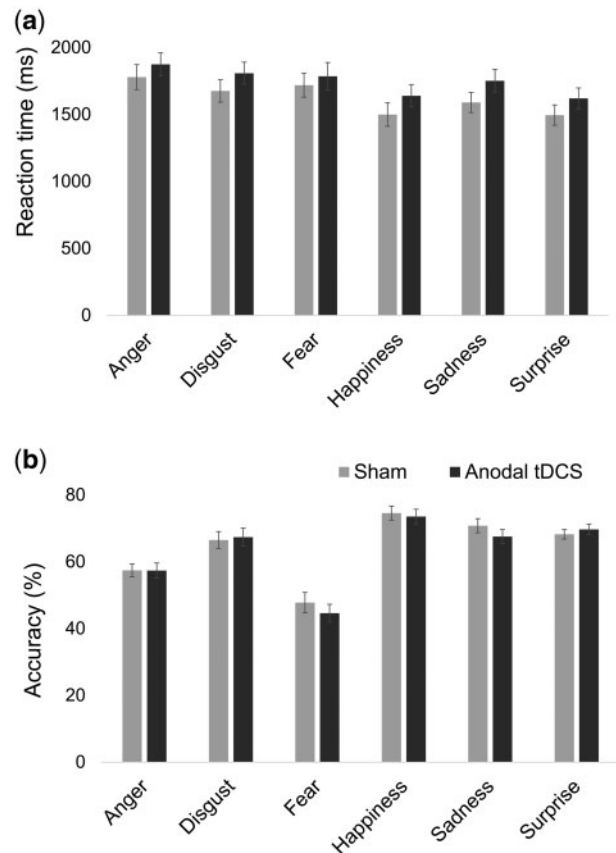
Fig. 3. Behaviour on the emotion task. **(a)** Mean reaction times by emotion category. Sham stimulation (light grey bars), was associated with shorter reaction times across all emotions on average than anodal tDCS stimulation (dark grey bars) (P = 0.017). **(b)** Mean percent accuracy by emotion category. There was no significant difference in accuracy between sham stimulation and anodal tDCS stimulation. Error bars represent standard errors of the mean.

($t(72)=6.70$, $p<0.001$), happy ($t(72)=8.68$, $p<0.001$), sad ($t(72)=8.30$, $p<0.001$), and surprise ($t(72)=7.59$, $p<0.001$). Anger was also identified significantly less accurately than: disgust ($t(72)=3.87$, $p<0.001$), sad ($t(72)=5.76$, $p<0.001$), happy ($t(72)=6.58$, $p<0.001$) and surprise ($t(72)=5.84$, $p<0.001$). Disgust was identified significantly less accurately than happy ($t(72)=2.67$, $p=0.009$), but not sad ($t(72)=1.07$, $p=0.290$) or surprise ($t(72)=0.91$, $p=0.367$); while happy was identified significantly more accurately than surprise ($t(72)=2.1$, $p=0.039$), but not sad ($t(72)=1.86$, $p=0.068$).

We did not find a significant stimulation-by-emotion interaction ($F(1,72)=1.33$, $p=0.25$). Bayes factor analysis revealed that the full model including both main effects and the stimulation-by-emotion interaction ($\log BF_{10}=99.12$) scored 1,468 times (decisively) worse than the winning model, which contained only the effect of emotion.

The slowing effect of tDCS on emotional face identification did not correlate with either the severity or frequency of side effects, using both Frequentist and Bayesian correlation analyses. In both cases, we calculated the difference in severity and number of side effects between active and sham conditions, and tested its association with the slowing effet of tDCS on emotional face identification (severity: Pearson's $r(45)=0.051$, $p=0.737$, $\log BF_{10}=-0.707$; frequency: $r(45)=0.205$, $p=0.178$,

logBF$_{10}$=-0.349). These correlations were only performed in the subset of participants who completed a systematic side-effects questionnaire (Brunoni *et al.*, 2011); 30 participants were not included in this analysis because we only recorded spontaneous reports of side-effects in that subset.
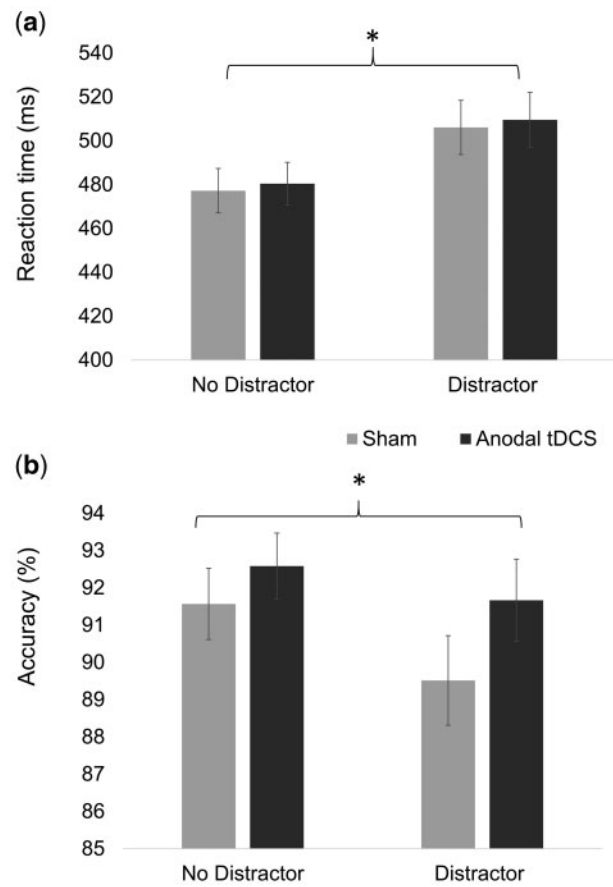
Distraction task

There was a significant stimulation-by-order interaction for both reaction time (F(1,29)=12.33, p=0.001) and accuracy (F(1,29)=10.04, p=0.004). These results represent practice effects by which participants performed faster and more accurately on the second testing session. Additionally, the evidence for models incorporating the stimulation-by-order interaction was higher than for those without. Therefore order (and where relevant the stimulation-by-order interaction) was retained in both Frequentist and Bayesian models.

Task-unrelated thought (TUT) responses had a highly skewed distribution, so we employed a non-parametric Wilcoxon Signed-Ranks Test. This showed that task-unrelated thoughts increased under real stimulation relative to sham, though this effect narrowly missed statistical significance (Z = 1.84, p = 0.067).

Effect of tDCS and distraction on reaction times. As expected, distraction significantly slowed responses (F(1,29)=65.6, p < 0.001; Figure 4a). There was no main effect of stimulation on reaction times (F(1,29)=0.059, p = 0.81), and no interaction between stimulation and distraction condition (F(1,29)=0.35, p = 0.56). By contrast, in the Bayesian analyses, the winning model contained main effects of distraction, stimulation and order, and the stimulation-by-order interaction (logBF$_{10}$=23.46), which scored 257 times (decisively) better than the model containing only the main effects of distraction and order (logBF$_{10}$=17.91). The apparent discrepancy between the Frequentist and Bayesian analyses here likely arises due to the inclusion of the term representing the practice effect (stimulation-by-order interaction), which adds substantial explanatory power to the more complex model. We additionally examined whether subjective ratings of mind-wandering were associated with slower reaction times in the distractor condition, but could not confirm this hypothesis using either Frequentist or Bayesian analyses (for real stimulation: r(31)=0.037, p = 0.903, logBF10=-1.480; for sham stimulation: r(31)=-0.023, p = 0.842, logBF10=-1.492).

Effect of tDCS and distraction on accuracy. tDCS significantly improved overall accuracy compared with sham stimulation (F(1,29)=7.30, p = 0.011, Figure 4b), and distraction significantly impaired accuracy (F(1,29)=5.46, p = 0.027). No significant interaction was found between stimulation and distraction condition (F(1,29)=0.92, p = 0.345, Figure 4b). The winning Bayesian model contained main effects of distraction condition, stimulation and order, and the stimulation-by-order interaction (logBF$_{10}$=2.75, strong evidence), which scored 23 times (strongly) better than the model containing only the main effects of distraction and order (logBF$_{10}$=-0.39).

Relationship between distractibility and emotion identification latency. We calculated a variable reflecting the effect of anodal tDCS on distractibility as assessed by reaction times (RTs). This was essentially the interaction effect between distractibility and tDCS: distractibility (distractor – no distractor condition RT) under real tDCS minus distractibility (distractor – no distractor condition RT) under sham tDCS. This enabled us to test whether

Fig. 4. Behaviour on the distraction task. (a) The effects of tDCS and distraction condition on reaction times. As expected, the condition with distractors elicited significantly slower responses (*p < 0.001), but there was no significant effect of tDCS on reaction times. (b) The effects of tDCS and distraction condition on accuracy. The presence of distractors decreased accuracy (*P = 0.027), and accuracy was higher in the anodal tDCS (dark grey bars) condition than in the sham (light grey bars) condition (*P = 0.011), but the interaction was non-significant. Error bars represent standard errors of the mean.

the effect of tDCS on lengthening reaction times on the emotional face identification task was driven by its effect on distractibility. We found that the extent to which tDCS slowed responses to emotional faces correlated positively with the increase in distractibility under tDCS (r = 0.37, p = 0.043; Figure 5). However, this was not unambiguously confirmed by the Bayesian analysis (log BF$_{10}$ = 0.47, inconclusive evidence).

Discussion

The main aim of this experiment was to test whether DLPFC tDCS affected hot and cold cognitive processing. We first investigated whether anodal DLPFC tDCS had acute effects on emotion identification. We hypothesized that tDCS might have an effect similar to antidepressant drugs, improving or speeding responses to positively-valenced faces, and/or impairing or slowing responses to negatively-valenced faces. We did not find this predicted interaction in either reaction times or accuracy scores. Instead, we identified a significant slowing of responses by tDCS on average across all emotional conditions; and using Bayes factor analysis, we found decisive evidence against an interaction between tDCS and emotion.
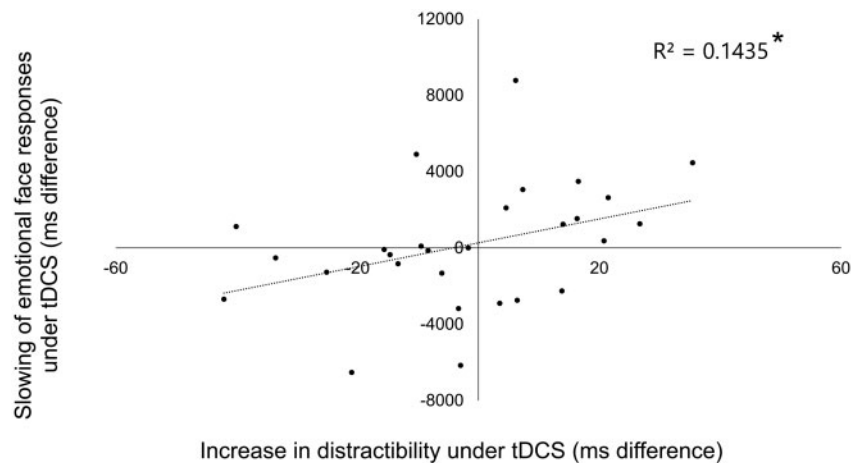
Fig. 5. Relationship between tDCS effects on latency to identify emotional faces and distractibility. There was a positive relationship between increased distractibility (the increase in reaction time in the distractor condition, relative to the no-distractor condition, on the distractibility task) under tDCS, and increased reaction times on the emotional faces task under tDCS. *P = 0.043.

This suggests that tDCS did not have a valence-specific effect on emotional face identification. Additionally, we did not identify a corresponding improvement in accuracy (i.e., a speed/accuracy trade-off) as a result of tDCS; in other words, participants became slower, but not better, at categorizing faces. Instead, this pattern of results indicates that tDCS has an effect on emotional deliberation, possibly making participants more uncertain about what emotional category a face belongs to.

In a subset of our participants, we tested a specific hypothesis that anodal DLPFC tDCS has an effect on distraction, using a task with the ability to index distractibility during real and sham tDCS sessions. We found preliminary results indicating that those participants whose distractibility increased most under tDCS were also those who showed an increased latency in the emotion identification task under tDCS (though we note that this could not be confirmed using Bayesian statistics). This task, which has previously been shown to correlate with internal distraction from mind-wandering (Forster and Lavie, 2014), also enabled us to test the basic effect of tDCS on distractibility with somewhat surprising results. We found that overall accuracy increased significantly under anodal tDCS, but that distractibility itself was not affected, which was confirmed by Bayesian analysis. Significantly improved accuracy under anodal tDCS is consistent with the finding that anodal tDCS over the frontal cortex increases alertness (Coffman *et al.*, 2014), perhaps by enhancing vigilance (Nelson *et al.*, 2014). However, it should be noted that the behavioural effects of tDCS vary substantially between studies (Tremblay *et al.*, 2014), causing some authors to cast doubt on the effects of tDCS on cognition altogether (Horvath *et al.*, 2015).

Relationship to mind-wandering in depression

Our findings suggest that tDCS does not instantiate a positive emotional bias in emotion identification, unlike antidepressant medication . Instead, our findings implicate cold cognitive processes in the acute effects of tDCS. The possibility that attentional mechanisms, such as distractibility, might mediate the effects of tDCS has particular implications for treating attentional symptoms of depression. Two previous studies reported increased mind-wandering (task-unrelated thoughts) under anodal tDCS of the DLPFC (Axelrod *et al.*, 2015) and left PFC (Kajimura and Nomura, 2015), although in our study this effect

narrowly missed statistical significance. However, the relationship between the recently-described effect of tDCS on self-reported mind-wandering (Axelrod *et al.*, 2015) and its putative antidepressant effects has so far been unexplored. Some studies have supported the notion that negative mood increases task-unrelated thoughts (Smallwood *et al.*, 2007), enhancing focus on task-irrelevant personal concerns; indeed, mind-wandering has even been suggested as a marker for ruminative thinking (Smallwood *et al.*, 2007). Yet there seems to be an inherent contradiction in the notion that mind-wandering is increased in depression (Smallwood *et al.*, 2007), that tDCS increases mind-wandering (Axelrod *et al.*, 2015), and that tDCS is an effective treatment for depression (Shiozawa *et al.*, 2014).

One possible resolution to this apparent contradiction lies in whether mind-wandering is truly a unidimensional phenomenon. While mind-wandering is typically measured in a binary way (e.g., 'Have you had any task-unrelated thoughts?'), it is much more likely that factors such as the valence of mind-wandering or *when* the mind wanders affect the subjective experience. For example, if mind-wandering occurs in a distressing environment, or while trapped in a train of negative thought, then it may be adaptive and useful. This idea is supported by a finding that mind-wandering itself does not precede the onset of depressive thoughts (though the inverse is true): only affectively negative mind-wandering has mood dampening effects (Poerio *et al.*, 2013). Since we did not test depressed patients, our study cannot address whether the tendency of tDCS to increase mind-wandering is related to its putative antidepressant effects. It will be important to test this hypothesis in future studies.

Limitations

Two important caveats to our results bear mentioning: first, the reaction time measurement in this task involved a fairly complex motor action (moving the mouse to click), and may differ substantially from more typical (highly speeded) reaction time measurements. This limits our ability to draw parallels with other reaction time tasks, though would not affect the differences we report between sham and anodal stimulation. Additionally, although we employ a typical tDCS montage used in depression (anodal left DLPFC stimulation), we specifically recruited healthy controls. It would be essential to replicate these

findings in a depressed sample to make stronger conclusions about the role of cold cognition and distractibility in tDCS for depression. We also note that, while our finding of a lack of emotional bias induced by tDCS was robust, the observed relationship between slowing of emotional identification and distractibility was weak and should be interpreted with caution. In particular, we cannot rule out the possibility that the latter correlation might reflect a generic disruptive effect of tDCS on the demanding aspects of cognitive and emotional tasks, which requires testing in future studies.

Conclusion

Few previous studies have investigated the effects of tDCS on hot and cold cognition, though both are thought to contribute to the pathogenesis of depression (American Psychiatric Association, 2003), and are associated with response to antidepressant medication (Potter *et al.*, 2004). We show that a tDCS montage commonly used in depression trials does not affect hot cognition, but may slow emotion identification by increasing distractibility. This finding suggests that the antidepressant effects of tDCS may result from different cognitive mechanisms than antidepressant medication.

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References

American Psychiatric Association (2003). Diagnostic and Statistical Manual of Mental Disorders. DSM-5 (ManMag).

Andrews, S.C., Hoy, K.E., Enticott, P.G., Daskalakis, Z.J., Fitzgerald, P.B. (2011). Improving working memory: the effect of combining cognitive activity and anodal transcranial direct current stimulation to the left dorsolateral prefrontal cortex. *Brain Stimulation*, **4**, 84–9.

Axelrod, V., Rees, G., Lavidor, M., Bar, M. (2015). Increasing propensity to mind-wander with transcranial direct current stimulation. *Proceedings of the National Academy of Sciences of the United States of America*, **112**, 3314–9.

Bamford, S., Penton-Voak, I., Pinkney, V., Baldwin, D.S., Munafò, M.R., Garner, M. (2015). Early effects of duloxetine on emotion recognition in healthy volunteers. *J. Psychopharmacol. (Oxf.)*, **29**, 634–41.

Baxter, L.R., Schwartz, J.M., Phelps, M.E., *et al.* (1989). Reduction of prefrontal cortex glucose metabolism common to three types of depression. *Archives of General Psychiatry*, **46**, 243–50.

Biver, F., Goldman, S., Delvenne, V., *et al.* (1994). Frontal and parietal metabolic disturbances in unipolar depression. *Biological Psychiatry*, **36**, 381–8.

Boggio, P.S., Rigonatti, S.P., Ribeiro, R.B., *et al.* (2008). A randomized, double-blind clinical trial on the efficacy of cortical direct current stimulation for the treatment of major depression. *International Journal of Neuropsychopharmacology*, **11**, 249–54.

Bradley, B., Mathews, A. (1983). Negative self-schemata in clinical depression. *British Journal of Clinical Psychology*, **22**, 173–81.

Brunoni, A.R., Amadera, J., Berbel, B., Volz, M.S., Rizzerio, B.G., Fregni, F. (2011). A systematic review on reporting and assessment of adverse effects associated with transcranial direct current stimulation. *International Journal of Neuropsychopharmacology*, **14**, 1133–45.

Brunoni, A.R., Valiengo, L., Baccaro, A., *et al.* (2013). The sertraline vs electrical current therapy for treating depression clinical study: results from a factorial, randomized, controlled trial. *JAMA Psychiatry*, **70**, 383–91.

Brunoni, A.R., Moffa, A.H., Fregni, F., *et al.* (2016). Transcranial direct current stimulation for acute major depressive episodes: meta-analysis of individual patient data. *British Journal of Psychiatry*, **208**, 522–31.

Coffman, B.A., Clark, V.P., Parasuraman, R. (2014). Battery powered thought: enhancement of attention, learning, and memory in healthy adults using transcranial direct current stimulation. *Neuroimage*, **85**, 895–908.

Drevets, W.C., Price, J.L., Furey, M.L. (2008). Brain structural and functional abnormalities in mood disorders: implications for neurocircuitry models of depression. *Brain Structure & Function*, **213**, 93–118.

Fales, C.L., Barch, D.M., Rundle, M.M., *et al.* (2009). Antidepressant treatment normalizes hypoactivity in dorsolateral prefrontal cortex during emotional interference processing in major depression. Journal of Affective Disorders, **112**, 206–11.

Forster, S., Lavie, N. (2008). Failures to ignore entirely irrelevant distractors: The role of load. *Journal of Experimental Psychology*, **14**, 73.

Forster, S., Lavie, N. (2014). Distracted by your mind? Individual differences in distractibility predict mind wandering. *Journal of Experimental Psychology: Learning, Memory, and Cognition*, **40**, 251.

Fregni, F., Boggio, P.S., Nitsche, M.A., Marcolin, M.A., Rigonatti, S.P., Pascual-Leone, A. (2006). Treatment of major depression with transcranial direct current stimulation. *Bipolar Disorder*, **8**, 203–4.

Galynker, I.I., Cai, J., Ongseng, F., Finestone, H., Dutta, E., Serseni, D. (1998). Hypofrontality and negative symptoms in major depressive disorder. *Journal of the Society of Nuclear Medicine*, **39**, 608–12.

Harmer, C.J., Hill, S.A., Taylor, M.J., Cowen, P.J., Goodwin, G.M. (2003). Toward a neuropsychological theory of antidepressant drug action: increase in positive emotional bias after potentiation of norepinephrine activity. *American Journal of Psychiatry*, **160**, 990–2.

Harmer, C.J., O'Sullivan, U., Favaron, E., *et al.* (2009a). Effect of acute antidepressant administration on negative affective bias in depressed patients. *American Journal of Psychiatry*, **166**, 1178–84.

Harmer, C.J., Goodwin, G.M., Cowen, P.J. (2009b). Why do antidepressants take so long to work? A cognitive neuropsychological model of antidepressant drug action. *British Journal of Psychiatry*, **195**, 102–8.

Harvey, P.O., Fossati, P., Pochon, J.B., *et al.* (2005). Cognitive control and brain resources in major depression: an fMRI study using the n-back task. *Neuroimage*, **26**, 860–9.

Horvath, J.C., Carter, O., Forte, J.D. (2014). Transcranial direct current stimulation: five important issues we aren't

discussing (but probably should be). *Frontiers in Systems Neuroscience*, **8**.

Horvath, J.C., Forte, J.D., Carter, O. (2015). Quantitative review finds no evidence of cognitive effects in healthy populations from single-session transcranial direct current stimulation (tDCS). Brain Stimulation, **8**, 535–50.

Ironside, M., O'Shea, J., Cowen, P.J., Harmer, C.J. (2015). *Frontal cortex stimulation reduces vigilance to threat: implications for the treatment of depression and anxiety*. Biological Psychiatry.

Jasper, H.H. (1958). The ten twenty electrode system of the international federation. *Electroencephalography and Clinical Neurophysiology*, **10**, 371–5.

Jeffreys, H. (1961). *Theory of Probability*, 3 ed. Oxford University Press.

Kajimura, S., Nomura, M. (2015). Decreasing propensity to mind-wander with transcranial direct current stimulation. *Neuropsychologia*, **75**, 533–7.

Koenigs, M., Grafman, J. (2009). The functional neuroanatomy of depression: distinct roles for ventromedial and dorsolateral prefrontal cortex. *Behavioural Brain Research*, **201**, 239–43.

Lally, N., Nord, C.L., Walsh, V., Roiser, J.P. (2013). Does excitatory fronto-extracerebral tDCS lead to improved working memory performance?

Loo, C.K., Alonzo, A., Martin, D., Mitchell, P.B., Galvez, V., Sachdev, P. (2012). Transcranial direct current stimulation for depression: 3-week, randomised, sham-controlled trial. *British Journal of Psychiatry*, **200**, 52–9.

Murphy, S., Downham, C., Cowen, P., Harmer, C. (2008). Direct effects of diazepam on emotional processing in healthy volunteers. *Psychopharmacology (Berl.)*, **199**, 503–13.

Nelson, J.T., McKinley, R.A., Golob, E.J., Warm, J.S., Parasuraman, R. (2014). Enhancing vigilance in operators with prefrontal cortex transcranial direct current stimulation (tDCS). *Neuroimage*, **85**, 909–17.

Nitsche, M.A., Koschack, J., Pohlers, H., Hullemann, S., Paulus, W., Happe, S. (2012). Effects of frontal transcranial direct current stimulation on emotional state and processing in healthy humans. *Frontiers in Psychiatry*, **3**.

Nolen-Hoeksema, S., Morrow, J. (1993). Effects of rumination and distraction on naturally occurring depressed mood. *Cognition and Emotion*, **7**, 561–70.

Nord, C.L., Roiser, J. (2015). Non-invasive direct current brain stimulation: the evidence behind the hype. *Advances in Clinical Neuroscience & Rehabilitation*, **15**, 9–11.

Poerio, G.L., Totterdell, P., Miles, E. (2013). Mind-wandering and negative mood: Does one thing really lead to another? *Consciousness and Cognition*, **22**, 1412–21.

Potter, G.G., Kittinger, J.D., Ryan Wagner, H., Steffens, D.C., Ranga Rama Krishnan, K. (2004). Prefrontal neuropsychological predictors of treatment remission in late-life depression. *Neuropsychopharmacology*, **29**, 2266–71.

Priori, A., Mameli, F., Cogiamanian, F., *et al.* (2008). Lie-specific involvement of dorsolateral prefrontal cortex in deception. Cerebral Cortex, **18**, 451–5.

Robinson, O.J., Bond, R.L., Roiser, J.P. (2015). The impact of threat of shock on the framing effect and temporal discounting: executive functions unperturbed by acute stress?. *Frontiers in Psychology*, **6**.

Roiser, J.P., Sahakian, B.J. (2013). Hot and cold cognition in depression. *CNS spectrums*, **18**, 139–49.

Roiser, J.P., Elliott, R., Sahakian, B.J. (2012). Cognitive mechanisms of treatment in depression. *Neuropsychopharmacology*, **37**, 117–36.

Shiozawa, P., Fregni, F., Benseñor, I.M., *et al.* (2014). Transcranial direct current stimulation for major depression: an updated systematic review and meta-analysis. *International Journal of Neuropsychopharmacology*, **17**, 1443–52.

Skinner, A.L., Benton, C.P. (2010). Anti-expression aftereffects reveal prototype-referenced coding of facial expressions. *Psychological Science*.

Smallwood, J., O'Connor, R.C., Sudbery, M.V., Obonsawin, M. (2007). Mind-wandering and dysphoria. *Cognition and Emotion*, **21**, 816–42.

Tremblay, S., Lepage, J.F., Latulipe-Loiselle, A., Fregni, F., Pascual-Leone, A., Théoret, H. (2014). The uncertain outcome of prefrontal tDCS. *Brain Stimulation*, **7**, 773–83.

Vanderhasselt, M.A., De Raedt, R., Brunoni, A.R., *et al.* (2013). tDCS over the left prefrontal cortex enhances cognitive control for positive affective stimuli. *PloS One*, **8**, e62219.

Wang, X.L., Du, M.Y., Chen, T.L., *et al.* (2015). Neural correlates during working memory processing in major depressive disorder. Prog. *Neuro-Psychopharmacology and Biological Psychiatry*, **56**, 101–8.

Wolkenstein, L., Plewnia, C. (2013). Amelioration of cognitive control in depression by transcranial direct current stimulation. *Biological Psychiatry*, **73**, 646–51.