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Title: When You Can, Scale Up: Large-Scale Study Shows No Effect of tDCS in an Ambiguous Risk-Taking Task.

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Keywords: transcranial direct current stimulation; prefrontal cortex; balloon analog risk task; decision making; risk; sample size; unilateral stimulation; bilateral stimulation; tDCS; BART

Corresponding Author: Mrs. Denise Wallace, MSc

Corresponding Author's Institution: University of Essex

First Author: Riccardo Russo, PhD

Order of Authors: Riccardo Russo, PhD; Paul C Twyman, MSc; Nicholas R Cooper, PhD; Paul B Fitzgerald, PhD; Denise Wallace, MSc

Abstract: Background: A wide range of neuroimaging and neuromodulation studies have shown that the dorsolateral prefrontal cortex (DLPFC) plays a pivotal role in decision-making. Of particular interest is the question of its role in decision-making when conditions are uncertain and whether manipulating this neural substrate through neuromodulation changes subsequent risk-taking behaviour. Previous work using the Balloon Analogue Risk Task (BART) suggests that bilateral tDCS stimulation of the DLPFC reduces risk-taking behaviour but unilateral stimulation has no effect. However, participant numbers have been limited and may have biased the estimate of the size of the effect of the stimulation on task performance.
Objectives/Hypothesis: We aimed to test the robustness and generalizability of these previous findings by using a very similar methodology but with a much larger sample.
Methods: During both 20- and 30-minute tDCS stimulation at 2 mA, we administered the BART to about 200 participants assigned to bilateral DLPFC stimulation of either right anodal/left cathodal, left anodal/right cathodal or sham (Study 1 and Study 2); and to unilateral stimulation conditions (Study 2): right anodal, left anodal or sham with the referent electrode over the contralateral supraorbital region.
Results: In the first bilateral study, we found that risk-taking was greater for participants in the right anodal/left cathodal stimulation group compared to those who received left anodal/right cathodal stimulation, but not compared to sham. The results obtained in the bilateral and unilateral stimulation protocols implemented in Study 2 yielded no evidence of any effect of stimulation. Combining the data from both studies, we found no statistically significant differences between mean performances of the nine stimulation groups. Indeed, all 95% confidence intervals for the nine means overlapped, suggesting that these randomly vary around a common population mean.

Conclusions: This study showed that there was no detectable effect of tDCS stimulation on risky decision-making under ambiguity, compared to sham stimulation. Hence, using a much larger sample, we did not replicate previous work reporting a reduction in risky decision-making by bilateral stimulation of the DLPFC compared to sham. When the results of our bilateral and unilateral stimulation studies were combined, it emerged that the most likely explanation for the apparent significant results in our bilateral stimulation study was random variation in performance. This outcome is a further reminder of the need for appropriately sized samples to potentially achieve reliable outcomes in brain modulation studies.

Cover Letter

04 August 2017

Dear Dr Badre,

We would like to re-submit our manuscript 'When You Can, Scale Up: Large-Scale Study Shows No Effect of tDCS in an Ambiguous Risk-Taking Task' for consideration.

We would like to thank the reviewers for considering our revisions and for their additional feedback. We very much appreciate it.

We have attached individual responses to the reviewer comments.

There are no conflicts of interest or any financial disclosure statement required for all authors with respect to the submitted study.

We look forward to hearing from you.

Best Regards,
Riccardo Russo
On behalf of the authors

Dear Reviewers,

Thank you very much for reviewing our revised manuscript. We are very grateful for your feedback and the time you have both spent doing so. We have provided our responses below.

Reviewer #1: I've only two words for the authors: here here!

C. It is clear your took the previous comments on board and (in my opinion) did the most truly scientific thing possible: undertook an additional study to address the reviewer concerns. I could honestly ask nothing more from you and am impressed with your dedication to the veracity of your arguments.

Great job.

PS - I think reviewer 2 gave you a rough shake: although I agree with many of his/her comments, it's a shame that the VAST majority of this field has not come even close to ticking all of those boxes. When a 'positive' result flies through unchecked whilst a 'null' result gets hounded for things like order effects and expectation effects, that is a sad state of affairs. As such, if the field doesn't expect this stuff from their 'stars', I can't see the benefit in expecting it from the rest. With that said, you addressed each well and convincingly in my opinion - now, if we could just get everyone else to follow your lead.....

A. Thank you very much for your positive feedback. We really appreciate it.

Reviewer #2: The authors satisfactorily addressed some of my comments in their response letter. There are still some to be addressed in the manuscript.

C1. Russo et al. aimed at testing whether tDCS has an impact on risk-taking. The main analyses must include only the stimulation groups. Please include this in both studies 1 and 2.

A1. We would like to point out that this remark is inconsistent with Reviewer 2's previous comments where he/she asked us for more comprehensive analyses to be reported. Please note that Reviewer 1 is happy with the way we have reported our analyses, which provide, inter alia, the main effect of stimulation.

C2. In the current version of the manuscript, the main analysis includes factors of N of balloons (they name it "Time") and stimulation groups. The authors should include their hypotheses in regards to the N of balloons.

A2. Reviewer 2 may not have realised that our prior version of the ms included the factor time, i.e. blocks of 10 balloons. We did not make any specific prediction on blocks since we tried to replicate a previous study.

C3.The label "Time" must be changed for "Sets of balloon". The term "Time" is typically used for pre-tDCS and post-tDCS. It could be misleading for the readers.

A3. We have changed "Time" to "Sets of balloons" throughout the manuscript.

C4. Please disclose all tasks that were administered (page 9 (line 58), page 10 (lines 22 and 27) and in Figures, etc.). This is a fundamental rule in science to fully disclose the methods. This does not prevent the authors from reporting results on these other cognitive tasks in other papers. In addition, if other teams wish to replicate Russo et al. results, they need the whole methods. Finally, if these other tasks did not have an impact on the BART performance, then this is a result in itself and should be reported.

A4. We have now provided all the tasks in the new Figure 2 (as per the recommendation in C6 below). We have also made adjustments in the manuscript text (page 10). The lack of statistically significant differences between Study 1 and Study 2 is evidence which demonstrates that task order did not have an effect on performance.

C5. Remove Figure 4 (the BART is already presented in Figure 1).

A5. Done.

C6. Remove Figure 2 and replace it with the supplemental Figure 1. They both illustrate Study 1 design and the supplemental one is more complete.

A6. Done.

C7. Add the Figure illustrating the Study 2 design (in the current version it is a supplemental Figure), which is important for the readers. The BART figure could be deleted as this is a well-known task.

A7. We have added the Study 2 design as Figure 3. We respectfully ask that Figure 1 remains in the manuscript as it shows a clear graphic display of what happened in Study 1.

C8. In regards to the sham protocol, the authors mention in their reply "we believe the 1 minute active stimulation did not have any impact". This should be discussed in the Discussion section, please specify that the sham protocol was 2 minutes of active stimulation (1 minute of 2mA plus a 30 sec ramp-up and a 30-sec ramp-down).

A8. Study 2 provided comparable results to Study 1 despite different sham exposure. We discussed our results in the context of the Fecteau et al. findings but see no benefit in highlighting that when participants received a longer active stimulation period during sham, we found no evidence of an effect on performance. We made all these methodological details explicit in the methods section. I have also added these details in the figures. The reader can clearly see that participants received 1 min 2 mA stimulation at the start of sham plus a 30 min ramp-up and ramp-down period which incrementally increased and decreased to the 2 mA current strength for Study 1. Likewise, 40 s 2 mA stimulation plus 30 s ramp-up and –down in Study 2.

C9. The "ON" display on this device means the device, not the current, is on for 30 minutes. Correct that it was a double-blind design (page 5).

A9. We accept that Reviewer 2's view is that "ON" display means that the device is on. However, a reasonable person would associate "ON" with the current flowing. For example, if a kettle is turned ON, then one would expect the water to boil. The exact wording in the Fecteau et al. paper reads: "The device used, developed by our group, is particularly reliable for double-blind studies: a switch can be activated to interrupt the electrical current while maintaining the "ON" display and showing the stimulation parameters throughout the procedure to the experimenter and participant."
We have amended the sentence to read that Fecteau and colleagues conducted their study in a double-blind manner (see page 5).

C10. Throughout the manuscript the authors report that they used a similar methodology as the one used in Fecteau et al. (e.g., "To this aim, we used a similar methodology to that employed by Fecteau and Colleagues…" page 7; "Overall, then our methodology was in principle appropriate to obtain results comparable to those of Fecteau and colleagues" page 28). Please re-write these sentences to be more accurate as there are methodological differences.

A10. "To this aim, we used a similar methodology to that employed by Fecteau and Colleagues…" We did not employ methods identical to Fecteau and colleagues, therefore we described the methods as similar. This implies that there were some differences. We conducted a new study (Study 2) to address these methodological differences which we made clear when introducing Study 2. Moreover, we have done our best to allow the reader to discern from the descriptions and figures provided with respect to how Study 1 differed from Study 2 and how our research differed from that of Fecteau and colleagues. We have adjusted the reference made on page 28 to remind the reader that the methodologies were not the same (see page 28).

C11 In addition, please include a section in the Discussion to clearly report methodological differences:

C11a- 2-min vs. 30 sec sham tDCS;

A11a – We respectfully argue that this would be inaccurate. We did not administer 2 min of 2mA in sham mode as this would mean there was no ramp-up or –down. The 30 s ramp-up and 30 s ramp-down period formed part of our tDCS protocol to very gradually increased and decreased current strength to 2 mA. Furthermore, we did not want to draw attention to the fact that Fecteau and colleagues regrettably didn't specify their ramp-up/down protocol (which could mean they didn't have one). It is likely that they had a dial that could be turned up to 2 mA, however without knowing for sure we would rather not publish a report with commentary regarding this particular aspect when it's not clear. We did our best to address the disparity in sham active stimulation duration in Study 2 by administering 20 min of stimulation instead of 30 min with a shorter sham active stimulation period (40 s vs 60 s). As we stated in our ms, our device, which is clinically approved, has an in-built sham activation program. For this reason we administered 40 s sham active stimulation with a 30 s ramp-up/down. It may be possible to manually remove the ramp-up/down feature and the sham active stimulation but for the safety and comfort of our participants we adhered to the device's in-built set-up. It is also our view that a 30 s ramp-up/down is very gradual, therefore allowing for a more subtle change to perceived sensation which is important for the well-being of the participant and for blinding.

C11b- Additional cognitive tasks were performed before the BART vs. no other cognitive tasks were performed;

A11b –We mentioned this difference when we introduced Study 2 (see page 14) and we addressed this issue by conducting Study 2 which had no additional cognitive tasks.

C11c- Subjects were told they would receive real tDCS; subjects were blinded to real/sham tDCS;

A11c – Yes, we led participants to expect active stimulation; participants agreed to be administered tDCS in the informed consent (which included information on the potential side effects of tDCS, etc.). We are not clear on how Fecteau and colleagues addressed this in their informed consent procedure. However, given the importance of ethics and the well-being of participants it is reasonable to assume that Fecteau and colleagues would have invited participants to agree in their informed consent to participate in a tDCS study (and what this entailed, including potential side effects). In addition, their participants were likely to have assumed that they would be administered active stimulation given that they could see the experimenter

turning on the device (with the parameters remaining consistent throughout the stimulation period). This would have been reinforced by the itching under the electrodes, which Fecteau and colleagues reported. We believe that although Fecteau and colleagues did not go into specifics of the stimulation with their participants, it would have probably been more accurate for them to have said in their report that they did not tell participants that they might receive sham. Ultimately, the fact that the machine showed "on" suggests to us that participants were lead to expect that they would receive active stimulation. See also A9. Again, we do not want to enter into a discussion on this point in our ms because Fecteau and colleagues didn't provide detailed information in their report about this aspect of their study.

C11d- Subjects were told they had 30 balloons vs. subjects were not told the N of balloons;

A11d – As above, the issue of whether N balloons was mentioned will have to remain a moot point without consulting the authors themselves. The original task, which Fecteau et al. referenced, clearly shows that the number of balloons are disclosed to participants in the instructions. If Fecteau and colleagues deviated from the classic task (Lejuez et al., 2002), we would reasonably expect them to state this in their report to allow other researchers to replicate their work more precisely.

C11d- Subjects performed the BART at various time points vs. subjects performed the BART at the same time point.

A11d – This issue was addressed by Study 2 where all participants completed the BART 5 min into stimulation.

C12 Horvath et al. (2016) did not test 200 participants per se. Specify it was a meta-analysis.

A12. We referenced Horvath, J. C., Carter, O., & Forte, J. D. (2016). No significant effect of transcranial direct current stimulation (tDCS) found on simple motor reaction time comparing 15 different simulation protocols. Neuropsychologia, 91, 544-552. This paper is original research, not a meta-analysis.

C13 In line with Horvath et al. (2016), this paper should be cited and discussed as it addresses meta-analyses of tDCS studies: Nitsche MA, Bikson M, Bestmann S. On the Use of Meta-analysis in Neuromodulatory Non-invasive Brain Stimulation. Brain Stimul. 2015 May-Jun;8(3):666-7.

A13. We thank Reviewer 2 for pointing out this paper, however it is not relevant to our report as we are not trying to summarise effects of tDCS in a meta-analytic manner.

C14This paper should be cited and discussed in line with their findings as it reviews studies using the BART: Brevet-Aeby et al. Prefrontal Cortex and Impulsivity: Interest of Noninvasive Brain Stimulation. Neurosci Biobehav Rev. 2016 Dec;71:112-34.

A14. We appreciate that Reviewer 2 has brought this research to our attention. In this review the only studies involving BART are those we have already cited, so there is no need to include it.

Highlights

- We aimed to assess whether neuromodulation affects risk taking
- tDCS applied to the dorsolateral prefrontal cortex does not affect risk taking
- Previous significant effects are likely to reflect random variation

When You Can, Scale Up: Large-Scale Study Shows No Effect of tDCS in an Ambiguous Risk-Taking Task.

Riccardo Russo[a]*, Paul Twyman[a] , Nicholas R. Cooper[a], Paul B. Fitzgerald[b] and Denise Wallace[a]*,

[a]Department of Psychology and Centre for Brain Science, University of Essex, Colchester, CO4 3SQ, UK

[b]Monash Alfred Psychiatry Research Centre, Monash University Central Clinical School and The Alfred, Monash University, Melbourne, Australia

* Corresponding authors:

Email address: rrusso@essex.ac.uk (RR); dwallace@essex.ac.uk (DW)

Words count: 9194

ABSTRACT

Background: A wide range of neuroimaging and neuromodulation studies have shown that the dorsolateral prefrontal cortex (DLPFC) plays a pivotal role in decision-making. Of particular interest is the question of its role in decision-making when conditions are uncertain and whether manipulating this neural substrate through neuromodulation changes subsequent risk-taking behaviour. Previous work using the Balloon Analogue Risk Task (BART) suggests that bilateral tDCS stimulation of the DLPFC reduces risk-taking behaviour but unilateral stimulation has no effect. However, participant numbers have been limited and may have biased the estimate of the size of the effect of the stimulation on task performance.

Objectives/Hypothesis: We aimed to test the robustness and generalizability of these previous findings by using a very similar methodology but with a much larger sample.

Methods: During both 20- and 30-minute tDCS stimulation at 2 mA, we administered the BART to about 200 participants assigned to bilateral DLPFC stimulation of either right anodal/left cathodal, left anodal/right cathodal or sham (Study 1 and Study 2); and to unilateral stimulation conditions (Study 2): right anodal, left anodal or sham with the referent electrode over the contralateral supraorbital region.

Results: In the first bilateral study, we found that risk-taking was greater for participants in the right anodal/left cathodal stimulation group compared to those who received left anodal/right cathodal stimulation, but not compared to sham. The results obtained in the bilateral and unilateral stimulation protocols implemented in Study 2 yielded no evidence of any effect of stimulation. Combining the data from both studies, we found no statistically significant differences between mean performances of the nine stimulation groups. Indeed,

all 95% confidence intervals for the nine means overlapped, suggesting that these randomly vary around a common population mean.

Conclusions: This study showed that there was no detectable effect of tDCS stimulation on risky decision-making under ambiguity, compared to sham stimulation. Hence, using a much larger sample, we did not replicate previous work reporting a reduction in risky decision-making by bilateral stimulation of the DLPFC compared to sham. When the results of our bilateral and unilateral stimulation studies were combined, it emerged that the most likely explanation for the apparent significant results in our bilateral stimulation study was random variation in performance. This outcome is a further reminder of the need for appropriately sized samples to potentially achieve reliable outcomes in brain modulation studies.

INTRODUCTION

Ernst and Paulus (2005, pg.1) define decision-making as "…the process of forming preferences, selecting and executing actions and evaluating outcomes". While research has consistently shown that decision-making involves the complex interplay between cognitive and emotional processes within the prefrontal cortex (PFC) and other closely interconnected neural networks, such as the limbic system (e.g. Ernst & Paulus, 2005; Slovic et al., 2004; Damasio,1996), the extent to which particular neural substrates are engaged, varies depending on a range of factors. These include the stage of decision-making (e.g. forming preferences vs. executing actions) (Ernst & Paulus, 2005), whether the decision's outcome is certain, risky or simply ambiguous (Krain et al., 2006) and whether the outcome probabilities of a risky decision are unknown or calculable by the individual (Fecteau et al., 2007; Rao et al., 2008; Fukunaga et al., 2012).

Of particular interest is that, across a wide range of risk-based tasks combined with neuroimaging and/or neurostimulation, the dorsolateral prefrontal cortex (DLPFC) has been shown to be pivotal to the process of risky decision-making (Guo et al., 2013; Cho et al., 2012, 2010; Rao et al., 2008; Fecteau et al., 2007; Krain et al., 2006; Knoch et al., 2006b, 2006a; van 't Wout et al., 2005). For example, studies using transcranial magnetic stimulation (TMS) on healthy volunteers have found that disrupting right DLPFC activity leads to increased risk taking (Knoch et al., 2006b), and that this particular area of the prefrontal cortex plays an important role in strategy (van 't Wout et al., 2005) and cognitive control (Knoch et al., 2006b, 2006a; Cho et al., 2012) in decision-making.

Fecteau and colleagues (2007) aimed to extend these findings by investigating whether modulating DLPFC activity using transcranial direct current stimulation (tDCS) would affect decision-making in ambiguous tasks (i.e. where the probability of the decision outcome is unknown). tDCS allows one to pass a mild current in the brain, and this

technique creates a more subtle excitatory/inhibitory effect compared to TMS and has been shown to be effective in both clinical and healthy populations (for review see Brunoni et al., 2012). tDCS differs from TMS in that the current field applied is not sufficient to cause the rapid depolarisation required to trigger an action potential but instead modulates the spontaneous neuronal network by de/hyperpolarizing the resting membrane potential of the stimulated neurons based upon the polarity of the field applied. This means that anodal stimulation has the general effect of enhancing cortical excitability under the area of the electrode, whilst cathodal stimulation reduces cortical activity under this electrode (Nitsche & Paulus, 2000).

Fecteau and colleagues (2007) used the Balloon Analogue Risk Task (BART), a well-established measure of risk (Lejuez et al., 2002), in two experiments. In the first, participants underwent double-blind bilateral stimulation of the DLPFC: one group with the right anodal electrode positioned on F4 according to the 10/20 EEG positioning method (Jasper, 1958) and the left cathodal electrode on F3; the second group with a right cathodal/left anodal montage, and the third group receiving sham stimulation (i.e. the placebo control condition). Their second study aimed to assess whether unilateral stimulation of the DLPFC could impact on decision-making under ambiguity; two groups of participants received either only right (F4) or left (F3) anodal stimulation with the cathodal electrode positioned over the contralateral supraorbital region. In both experiments the current strength was 2mA, delivered using 35cm^2 electrodes. Participants performed a Stroop task prior to and following stimulation. The BART task was executed in an on-line neuromodulation mode following an initial 5-minute 'warm-up' stimulation period where participants did not perform other tasks. The BART task was executed in less than 15 minutes. Participants were tested in a double-blind mode. In an overall analysis of their data, it emerged that both active bilateral stimulation groups (right anodal/left cathodal; left anodal/right cathodal), compared to sham,

led to a significant reduction in risk-taking behaviour, while unilateral stimulation led to results equivalent to the sham condition, thus adding to the literature suggesting that neuromodulation of the DLPFC directly impacts on decision making tasks' performance. The obtained results led the authors to conclude that only when an excitatory effect applied to one side of the DLPFC (anodal stimulation) is coupled with an inhibitory effect (cathodal stimulation) applied to the contralateral side, cautious behaviour emerges. Furthermore, they speculated that this was a consequence of the tDCS changing the balance of activity between the left and right DLPFC.

While Fecteau and colleagues' (2007) findings could potentially be relevant to refine our understanding of the role of DLPFC in decision-making, it is important to consider some potential caveats. Firstly, they tested a total of 47 participants across five conditions (reduced to 44 following the exclusion of three participants, whose performance fell outside two standard deviations from their group mean) in a between-groups design. Such a small sample size distributed over five conditions would increase the likelihood of obtaining a severely biased estimate of the effect size of a variable compared to the actual population parameter (e.g. Schönbrodt & Perugini, 2013). It is therefore unclear the extent to which the outcome of the study is reliable. Other studies assessing the impact of transcranial electrical stimulation on decision making tasks also appear to have used relatively small sample sizes, (e.g. Sela, Kilim & Lavidor, 2012**)** thus they may also suffer from the same potential issue. While it is relevant to assess the robustness and generalizability of the findings of those studies based on small samples, we will confine ourselves in this study to try to assess the robustness and generalizability of the finding of Fecteau et al.'s (2007), since this is one of the first and more influential studies on the impact of transcranial electrical stimulation on decision making.

To this aim, we used a similar methodology to that employed by Fecteau and colleagues and we tested a much larger sample. Finally, we measured the correlation between the Sensation Seeking Scale (SSS) (Zuckerman et al., 1964), the Eysenck Impulsiveness Scale (Eysenck et al., 1985) and the performance in the BART. As found by Lejuez and colleagues (2002), we predicted that participants scoring higher on sensation seeking measures were likely to score higher on the BART (i.e. to take a greater risk).

STUDY 1

METHODS AND MATERIALS

Participants

One hundred and seventeen healthy students (68 females) aged 18 to 30 years (M 21.14, SD 2.7; 5 left-handed) participated in Study 1 (bilateral stimulation). Using the data available in the Fecteau et al. study we tried to estimate the effect size (measured as Phi) for the main effect of the stimulation condition in their bilateral study, which appeared to be about 1. Assuming that this value provides a fair reflection of the size of the effect of the stimulation protocol on the BART at population level, our study would have a power greater than .95 (indeed a total sample of at least thirty-three participants would suffice to achieve this level of statistical power).

All participants confirmed that they did not have any mental health or neurological disorders, were not taking medications affecting the central nervous system and were naïve to the BART task. All participants gave written informed consent and received either a course credit or small payment for attending. No performance task related payments were given to participants. This study was approved by the University of Essex Faculty of Science and Engineering Ethics Committee.

tDCS Stimulation

We used a DC-Stimulator Plus (Neuroconn, Germany) with two 35 cm² (5 x 7 cm) conductive rubber electrodes inside saline-soaked sponges (NaCl concentration: 100 mM dissolved in distilled water). Due to an error, 20 participants in Study 1 were tested with 5 x 5 cm electrodes. As shown later the different sizes did not impact on the study outcome. The electrodes were secured using rubber straps and positioned over the DLPFC according to the International 10-20 system. In Study 1, participants were randomly assigned to one of three bilateral stimulation conditions: F4 right anodal/F3 left cathodal (n = 41); F3 left anodal/F4 right cathodal (n = 43) and sham (n = 33). Double-blinding was achieved using the "study mode" of the tDCS device. The sham setting aimed to produce similar sensory experiences as in those experienced in the verum conditions in order to mask the stimulation condition administered. In the active stimulation conditions, a current strength of 2 mA was applied for a total of 30 min with a ramp-up and ramp-down phase of 30 s. In the sham condition, ramp-up duration was 30 s followed by 1 min of 2 mA stimulation then a 30 s ramp-down. The duration of active stimulation during the sham period is automatically calculated by the DC-Stimulator Plus software: the active stimulation period (in seconds) is divided by 30 (i.e. 1800 s/30 = 60 s). Participants were told that they would be administered active stimulation. During stimulation, prior to completing any tasks, participants watched a nature video for 5 min to habituate to the stimulation.

Balloon Analogue Risk Task

Referring to Figure 1, participants were presented with a computer screen showing a balloon and a balloon pump button, which participants were required to press to inflate the balloon. Each pump accumulated 5c. There was also a box displaying "number of pumps on this balloon" and a box showing "$$$ so far on this balloon" (temporary bank). Participants could then transfer this money to a permanent bank and move on to the next balloon by

pressing the "COLLECT $$$" reset button. By pressing this button they would lose the opportunity to earn more money on the present trial, but also avoid the increasing probability that the balloon would explode. A box labelled "TOTAL SCORE" displayed the permanently banked money earned over the course of the task. Each balloon had a variable, randomised explosion point (1 to 128 out of 128) so the participant could not predict when the balloon would explode. If the balloon exploded before the participant had banked their money, all the money in the temporary bank was lost and a new balloon appeared. Pressing the "COLLECT $$$" button was accompanied by a slot machine sound. Balloon explosions were accompanied by an explosion sound. The task comprised 30 balloons (refer to Lejuez et al., 2002 for more detail).

Questionnaires

Participants completed the Sensation Seeking Scale (SSS) (Zuckerman et al., 1964,1978), comprising 40 forced-choice statements. These items measure self-reported sensation-seeking behaviours on 4 subscales: Disinhibition, Boredom Susceptibility, Thrill and Adventure Seeking and Experience Seeking plus a total score. These participants also completed the Impulsivity subscale of the Eysenck Impulsiveness Scale (EIS) (Eysenck et al., 1985), which comprises 19 impulsivity-related forced choice questions. For both questionnaires, a higher score indicates a greater propensity for sensation seeking and impulsivity, respectively. These tests were used to assess the extent to which measures of general risk taking would correlate with the scores in the BART task.

Procedure

Participants were told that they would receive 30 minutes of active stimulation whilst completing a number of cognitive tasks, including the BART. Participants were given all

task instructions prior to stimulation. The BART was explained using a printed-out copy of the on-screen instructions and Figure 1. Participants were told how many balloons there would be, how much each pump was worth and that the balloon might explode at any point from the first pump until it filled the entire computer screen. We asked participants to confirm that they understood the task and answered any questions. Once stimulation began, we asked the participants to read through the on-screen instructions and begin when ready. For practical reasons, participants completed the BART at different time points during stimulation depending on the individual experiment as set out in Figure 2. Specifically, for the majority of participants (i.e. 95) stimulation began with a 5-minute habituation period during which participants watched a nature video, followed by a 2-minute memory task, followed by the BART, while for the remaining 22 participants the same 5-minute habituation procedure preceded a questionnaire (5 min) followed by the Cambridge Task (15 min), followed by the BART. As shown in the analyses below this different arrangement did not affect performance in the BART task. Following stimulation, the electrodes were removed and participants completed the EIS then the SSS.

Data Analysis

There were two outcome measures for the BART: average adjusted pumps (i.e. for trials where the balloon did not explode); and total money earned. Average adjusted pumps is the clearest indicator of risk-taking behaviour of all the available measures in the BART, as individual differences are not constrained by an external event (balloon exploding) (Lejuez et al., 2002; Fecteau et al., 2007). Total money earned is usually directly related to the number of average adjusted pumps; these data will be analysed in the same manner as average adjusted pumps. Both variables were analysed as sets of balloons, with three levels: first, second and third sets of 10 balloons. The between-groups measure was stimulation

condition. Stimulation condition comprised three independent groups: right anodal/left cathodal; left anodal/right cathodal; sham. The Greenhouse-Geisser approach was used, when required, to adjust the p-value of interactions and main effects involving a within-subjects factor.

To explore the relationship between sensation seeking, impulsivity and risk propensity we conducted a Pearson product-moment correlation coefficient with the SSS, EIS and average (number of) adjusted pumps.

RESULTS

Data checks

The first 20 participants of the study were tested with 25 cm² electrodes. The remaining 97 participants were tested with 35 cm² electrodes. As in Bastani and Jaberzadeh (2013), who found no significant difference in the effect of 25 cm² and 35 cm² electrodes on a task tapping on the M1 region, our mixed ANOVA found that the mean overall performance between these two electrode size groups was comparable (32.90 vs. 32.79, respectively). In addition, the size of the electrodes did not interact significantly with the other variables (sets of balloons and electrode positions) on the average number of adjusted pumps ($F's < 1$), therefore the data from these early participants were retained (total n = 117). Ninety-five participants completed the BART seven minutes into the stimulation period, while 22 participants completed the BART twenty minutes into the stimulation period. This occurred because, as indicated earlier, some people were asked to perform other tasks than the BART in the experimental session. The overall mean performances in these two groups were comparable (33.23 vs. 31.41, respectively). A mixed ANOVA revealed no statistically significant main effects or interaction on the average number of adjusted pumps involving the different points in the experimental session at which the BART task was administered ($F's <$

1). The same analyses on the amount of money earned gave comparable outcomes. Hence, the data from all participants were used in the subsequent analyses.

Comparing the amount of time each stimulation group needed to perform the BART, we analysed stimulation conditions in a between-subjects comparison of mean duration. The means, in seconds, were 430.57; 420.06 and 406.46, for right anodal/left cathodal; left anodal/right cathodal and sham. A One-way ANOVA did not detect statistically significant differences between these means (F's (2, 114) < 1) indicating that the time taken to complete the BART was comparable regardless of the stimulation condition employed.

Participants most commonly reported itching, tingling or burning/stinging stimulation. A detailed report regarding perceived comfort which includes Study 1 was published separately (Russo et al., 2013). Although we did not assess experimenter blinding, we have published results which show that the double-blinding for participants, with additional masking provided by telling participants that they will receive active stimulation, is effective (Russo et al., 2013; Wallace et al., 2016).

Main analysis

Table 1 provides the descriptive statistics with respect to the average number of adjusted pumps and money earned. The main effects of sets of balloons ($F(2,228) = 49.28$, $MSE = 40.72$, $p < .0001$, $\eta_p^2 = .30$) and stimulation conditions ($F(2,114) = 3.39$, $MSE = 466$, $p = .037$, $\eta_p^2 = .056$) on average adjusted pumps were statistically significant; while there was no significant interaction between sets of balloons and stimulation conditions ($F(4,228) = 1.27$, $MSE = 40.72$, $p = .28$, $\eta_p^2 = .02$). Participants were most cautious in the first set of ten balloons (M = 28.2), becoming less so in the second (M = 34.1) and third sets (M=36.2), respectively. The significant effect of the stimulation conditions was associated with a larger number of pumps in the right anodal/left cathodal stimulation (M = 37.0), with a smaller

number of pumps in left anodal/right cathodal and sham conditions (M = 30.4 and M = 31.1, respectively). According to the Tukey HSD post-hoc test the mean difference between the number of pumps produced with right anodal/left cathodal stimulation was significantly larger than for the left anodal/right cathodal condition (p = .046), however neither group differed significantly from sham (p= .11 and p = .97, for right anodal/left cathodal and left anodal/right cathodal vs. sham, respectively). Analogous results were obtained with money earned as the dependent variable: The main effects of sets of balloons (F (2,228) = 22.01, MSE = 55697, p < .001, η_p^2= .16) and stimulation conditions (F (2,114) = 3.4, MSE = 284451, p = .037, η_p^2= .056) were statistically significant; while there was no significant interaction between sets of balloons and stimulation conditions (F (4,228) = 0.995, p =.41, η_p^2= .02). According to the Tukey HSD post-hoc test the amount of money gained with right anodal/left cathodal stimulation was significantly larger than for the left anodal/right cathodal condition (p = .03), however neither group differed significantly from sham (p= .27 and p = .67, for right anodal/left cathodal and left anodal/right cathodal vs. sham, respectively).

Correlational analyses of the SSS and the EIS with average adjusted pumps revealed a weak positive but significant relationship between SSS and average adjusted pumps scores (r = 0.216, p = 0.019). The correlation between EIS and average adjusted pumps was in the same direction but was not significant (r = 0.127, p = 0.17). Hence we replicated the positive correlation between the SSS output and average adjusted pumps detected in the seminal Lejuez and colleagues (2002) study. There was no significant difference between the scores in the SSS and in the EIS across the three stimulation conditions (F's < 1.81, p > .17).

Overall it appears that our study not only could not replicate the original results obtained by Fecteau et al., but, if anything, seemed to indicate that bilateral modulation of the DLPFC, at least using the right anodal/left cathodal stimulation, apparently increased risk taking, rather than decreased risk taking, as originally reported.

STUDY 2

There were methodological differences between our and Fecteau et al.'s studies, thus bringing into question the extent to which our methodology was, in principle, appropriate to obtain results comparable to those obtained by Fecteau et al. For example, in our study participants were not necessarily at rest during habituation (they watched a nature video rather than simply relaxing before the BART), in addition they did not perform the BART directly after the 5-minute habituation period (as in the Fecteau et al. study), but following another task. This is because the BART formed part of a wider cognitive study we were conducting (see Fig. 2 for the full procedure followed). These differences in procedure may have potentially lead to some form of uncontrolled state-dependency influence, whereby performing prior tasks may have influenced the impact of neuromodulation on subsequent tasks (Silvanto, Muggleton & Walsh, 2008), thus biasing the outcome of neuromodulation on the BART. While, in principle, these are relevant concerns, our preliminary analyses indicated that these issues did not affect the outcome of our study. For the avoidance of doubt we decided to repeat the Fecteau et al. study, adhering as closely as possible to the original methodology, on the basis of the information provided in the original study (see Fig 3). To this aim we planned to test 48 participants in the bilateral stimulation conditions previously described, moreover, to more closely mimic the procedure used by Fecteau et al., we also tested 33 participants to assess the impact of unilateral anodal stimulation on F3 and F4. Here, the referent cathodal electrode was placed over the contralateral supraorbital region. As previously indicated, this sample size is large enough to obtain a power of at least .95 on the assumption of a neuromodulation effect size of Phi = 1. Unlike Study 1 where during the execution of the BART a box displaying "number of pumps on this balloon" and a box showing "$$$ so far on this balloon" (temporary bank) were visible to participants, in Study

2, to more closely adhere to Fecteau et al. procedure, these boxes were not available to participants.

Finally, we also included the Stroop Task before and after stimulation. Fecteau and colleagues added this task to their study to assess whether there were any inhibitory effects on BART performance because of the potential for tDCS to co-activate neighbouring brain regions such as the orbitofrontal cortex. They found no impact of stimulation on the duration of task completion or performance for the BART or on the post-stimulation Stroop performance.

The above methodology, would not only allow a more stringent assessment of the generalizability of Fecteau et al.'s results, but might also help to clarify previous findings. Some research suggests that risky decision-making engages predominantly right-sided prefrontal neural substrates, the right DLPFC in particular (e.g. van 'tWout et al., 2005; Knoch et al., 2006a; Cho et al., 2010), while Fecteau and colleagues argued that decision-making in ambiguous tasks may require a balanced activity across hemispheres, thus the combined effect of left and right DLPFC processes are important to adaptive decision-making. If our attempted constructive replication of Fecteau and colleagues' bilateral results were to be successful, one possible outcome for our unilateral study would be no statistically significant differences between unilateral stimulation groups in combination with a significant difference with the bilateral stimulation conditions, when the data from all stimulation conditions are compared. This outcome would support the "balanced activity" argument. In addition, the analysis of the outcome of the unilateral study also allows us to further assess the potential impact of the right-sided prefrontal neural substrate in ambiguous decision making tasks.

METHODS AND MATERIALS

Participants

Forty-eight healthy students (32 females) aged 18 to 28 years (M 21, SD 2.6; 0 left-handed) participated in the bilateral stimulation condition; while thirty-three healthy students (19 females) aged 18 to 31 years (M 20, SD 2.5; 0 left-handed) participated in the unilateral stimulation condition. The total sample comprised 81 participants. All participants confirmed that they did not have any mental health or neurological disorders and were not taking medications affecting the central nervous system. All participants were naïve to the BART task. All participants gave written informed consent and received either a course credit or small payment for attending. Participants were also told that the highest earner would receive a £30 gift voucher. This study was approved by the University of Essex Faculty of Science and Engineering Ethics Committee.

tDCS Stimulation

We used a DC-Stimulator Plus (Neuroconn, Germany) with two 35 cm^2 (5 x 7 cm) conductive rubber electrodes inside saline-soaked sponges (NaCl concentration: 100 mM dissolved in distilled water). The electrodes were secured using rubber straps and positioned over the DLPFC according to the International 10-20 system. As in Study 1, participants were randomly assigned to one of three bilateral stimulation conditions: F4 right anodal/F3 left cathodal (n = 16); F3 left anodal/F4 right cathodal (n = 16) and sham (n = 16): while the remaining thirty-three to: F4 right anodal/Supraorbital left cathodal (n = 11); F3 left anodal/ Supraorbital right cathodal (n = 11) and sham (n = 11). The study was double-blinded using the "study mode" of the tDCS device. In the active stimulation conditions, a current strength of 2 mA was applied for a total of 20 min with a ramp-up and ramp-down phase of 30 s. In the sham condition, ramp-up duration was 30 s followed by 40 s of 2 mA stimulation then a

30 s ramp-down. The duration of active stimulation during the sham period is automatically calculated by the DC-Stimulator Plus software: the active stimulation period (in seconds) is divided by 30 (i.e. 1200 s/30 = 40 s).

All participants were told that they would be administered active stimulation.

Stroop Task

The Stroop Test (Stroop 1935) is widely used to measure executive functions; in particular, processing speed and selective attention. Neuroimaging studies have shown that the DLPFC is involved in selective attention (Hadland et al., 2001, cited in Vanderhasselt et al., 2006). Hence, the purpose of the Stroop Task in this study is to assess potential impact of tDCS on prepotent response inhibition.

The Stroop Task software we used is the "Color Word Stroop with Keyboard Responding (English)" created by Inquisit version 4.0.9.0 for Windows. Four colours were administered (red, green, blue, black) within 3 colour-congruency levels (congruent, incongruent, control); each combination was run 7 times, totalling 84 randomised trials. Latencies were measured in milliseconds, from onset of stimuli. The inter-trial interval was 200 ms. The stimuli consisted of congruent/incongruent colour words as well as a control variable comprising rectangle shapes. The Stroop task was used by Fecteau et al. before and after participants performed the BART.

Balloon Analogue Risk Task

Participants were presented with a computer screen showing a balloon, a balloon pump button, a "COLLECT $$$" button and a box labelled "TOTAL SCORE". Participants were told that they could pump up the balloon and that each pump accumulated 5c in a temporary bank. For each balloon, participants could choose to stop pumping at any time and

transfer the money earned to a permanent bank by pressing the "COLLECT $$$" button. By pressing this button they would lose the opportunity to earn more money on the present trial, but also avoid the increasing probability that the balloon would explode and that they would lose the money already accumulated. Money earned over the course of the task was displayed in the box labelled "TOTAL SCORE". Each balloon had a variable, randomised explosion point (1 to 128 out of 128) so the participant could not predict when the balloon would explode. If the balloon exploded before the participant had banked their money, all the money in the temporary bank was lost and a new balloon appeared. Pressing the "COLLECT $$$" button was accompanied by a slot machine sound. Balloon explosions were accompanied by an explosion sound. The task comprised 30 balloons (refer to Lejuez et al., 2002 for more detail).

Data Analysis

The BART data was analysed as per Study 1, where average adjusted pumps and total money earned were the dependent variables and stimulation conditions was the independent variable.

The Stroop Task was administered before (time 1) and after (time 2) stimulation. We therefore analysed, as dependent variable, the median latency values for correct trials only, comparing time 1 and time 2. The independent variable was stimulation condition. Data were analysed separately for the bilateral and unilateral studies and then combined. We also analysed accuracy where number of errors, at time 1 and time 2, was the dependent variable. Stimulation condition was the independent variable. Given that our main focus is on the impact of tDCS stimulation, we primarily report detailed results of statistical analyses involving stimulation conditions for the Stroop Task.

Participants and the researcher were asked to judge whether they thought they had received active or sham stimulation. Here we compared actual stimulation condition against participant and researcher judgements using Chi Square.

Procedure

Participants were told that they would complete a colour-naming task before and after a 20-minute period of active stimulation and that during stimulation, they would relax for the first 5 minutes before completing a balloon task.

Participants gave informed consent after completing the screening questionnaires. The instructions for both tasks were then fully explained followed by the electrode placement. Once the electrodes were in place participants completed the Stroop Task followed by a comfort questionnaire. The stimulation device was then activated with a code provided by the principle investigator. A second comfort scale was administered after the initial 30 s ramp-up phase. Participants relaxed for the first 5 minutes. The BART was then administered. Thirty seconds before the end of the 20-minute stimulation period, participants completed a third comfort scale. At the same time, out of sight of the participant, the researcher completed a judgment questionnaire indicating whether the stimulation condition was believed to be active or sham. Directly following stimulation, the participant was asked to complete an identical on/off judgment questionnaire, followed by the Stroop Task. The electrodes were then removed and the skin was inspected.

RESULTS

As with Study 1, participants commonly reported tingling, burning/stinging or itching. Chi Square analysis for the bilateral (n = 48) and unilateral (n = 33) studies showed that neither participants (p's $\geq$ .74) nor the researcher (p $\geq$ .21) were able to accurately judge

whether real or sham stimulation had been received.

Balloon Analogue Risk Task

We report firstly the outcome of the bilateral and unilateral stimulation conditions then, as conducted in Fecteau and colleagues (2007), a further analysis was carried out combining both conditions. Data are summarised in Table 1.

Bilateral stimulation

The main effects of sets of balloons ((F (2,90) = 16.54, MSE = 50.2, p < .001, η_p^2= .27) was significant. Participants were most cautious in the first set of ten balloons (M = 25.9), becoming less so in the second (M = 31.5) and third sets (M = 34.0), respectively. While the main effect of stimulation conditions (F (2,45) = 0.04, MSE = 442, p = .96, η_p^2= .002) and the interaction between sets of balloons and stimulation conditions (F (4,90) = 0.4, MSE = 50.2, p =.74, η_p^2= .02) were not significant. Analogous results were obtained with money earned as the dependent variable: The main effects of sets of balloons was significant (F (2,90) = 9.3, MSE = 67578, p < .001, η_p^2= .17) , while stimulation conditions (F (2,45) = 0.02, MSE = 297119, p = .99, η_p^2= .0001) and the interaction (F (4,90) = 0.67, p =.29, η_p^2= .03) were not significant.

Unilateral stimulation

The main effect of sets of balloons (F (2,60) = 17.0, MSE = 44.99, p < .001, η_p^2= .36) was significant. Participants were most cautious in the first set of ten balloons (M = 26.7), becoming less so in the second (M = 34.9) and third sets (M = 35.3), respectively. While the main effect of stimulation conditions (F (2,30) = 0.91, MSE = 371, p = .41, η_p^2= .057) and

the interaction between sets of balloons and stimulation conditions (F (4,90) = 1.95, MSE = 44.99, p = .11, η_p^2= .11) were not significant. Comparable results were obtained with money earned as the dependent variable: The main effect of sets of balloons was significant (F (2,60) = 12.1, MSE = 49707, p < .001, η_p^2= .29). The main effect of stimulation conditions (F (2,30) = 0.95, MSE = 209667, p = .40, η_p^2= .059) was not significant, while the interaction (F (4,60) = 2.77, MSE = 52972, p =.039, η_p^2= .156), unlike the results for the averaged adjusted pumps, reached significance. The significance of the interaction is mainly attributable to lower earnings in the sham in the first set of ten balloons compared to the active stimulation conditions then reversing for the second and third set where higher earnings occurred in the sham conditions.

Bilateral and unilateral stimulations combined

In the mixed ANOVA conducted combining all the data on the average adjusted pumps, we found a statistically significant main effect of sets of balloons (F (2,150) = 32.2, MSE = 48.1, p < 0.001, η_p^2= .38) indicating an increase in the number of pumps across set 1 to set 3. The interaction (F (10,150) = 1.04, MSE = 48.1, p = .41, η_p^2= .065), and the main effect of stimulation were not significant (F (5,75) = 0.44, MSE = 413, p = .82, η_p^2= .03), with means ranging from 29.8 (sham bilateral) to 35.2 (left anodal, unilateral). Comparable results were obtained for money earned with a significant main effect of sets of balloons (F (2,150) = 18.22, MSE = 60430 , p < 0.001, η_p^2= .195) and a non-significant interaction F (10,150) = 1.63, MSE = 60430, p = .11, η_p^2= .098). The main effect of stimulation was also not significant (F (5,75) = 0.35, MSE = 262138, p = .88, η_p^2= .023).

A further analysis was also carried out on the effect of stimulation conditions on averaged adjusted pumps including the data from the first study (N = 198). It now emerges that the effect of stimulation conditions, unlike when only the data from Study 1 were analysed, is no longer significant (F (8,189) = 1.25, MSE = 445.1, p = .27, η_p^2= .05). Hence, despite the significant ANOVA in the first study could have lent to the supposition that greater risk taking is associated to bilateral right anodal/left cathodal stimulation, when the data from all nine stimulation conditions are compared there is no significant effect of modulation. Indeed, as noticeable in the graph in Figure 4, providing the means of the nine conditions with their 95% confidence interval, all confidence intervals overlap each other, thus implying that the nine means may well randomly vary around a common population mean. Therefore, the most likely explanation for the outcome of Study 1 is a Type 1 error.

The above conclusion is further reinforced by the following observation/thought experiment. Imagine that, in considering only Study 2, there would be a significant difference among the means. If so, it would then appear that the higher level of risk would be associated with unilateral left anodal stimulation (see Fig. 4). However, any prediction arising on the basis of the outcome of Study 1, where right anodal/left cathodal stimulation was associated with greater risk taking, would not suggest that in a subsequent experiment using unilateral stimulation, the left anodal stimulation condition would be the one leading to higher risk taking. Overall, then, it appears that the numerical difference in the means of the average adjusted pumps across all stimulation conditions employed in the two studies is imputable to random variation rather than different stimulation montages.

Stroop Task

As with the BART, we report the results for the bilateral stimulation study, followed by the unilateral study and then the two studies combined. Descriptive data for the Stroop

Task are presented in Table 2 and response latencies (measured in milliseconds) by stimulation condition by time are presented in Figure 5.

Bilateral stimulation

We conducted a mixed ANOVA with time (time 1; time 2) and congruency (congruent; incongruent; control) as within-subjects variables and stimulation conditions (right anodal/left cathodal; left anodal/right cathodal; and sham) as between subjects variable. The main effect of time ((F (1,45) = 82.28, MSE = 25074.15, $p < 0.001$, $\eta_p^2 = .65$) was statistically significant; participants were quicker at time 2 (M = 718.24) compared to time 1 (M = 887.51). The main effect of congruency (F (2,90) = 60.07, MSE = 13299.82, $p < 0.001$, $\eta_p^2 = .57$) was also statistically significant; response latencies were longest for incongruent stimuli (M = 907.80) followed by control stimuli (M = 758.51) while congruent stimuli (M = 742.32) yielded the shortest latencies.

The time by stimulation conditions, congruency by stimulation conditions and the time by congruency by stimulation conditions interaction effects were not statistically significant ($F's \leq 2.5$, $p's > .09$). The main effect for stimulation conditions was also not statistically significant (F (2,45) = 1.10, MSE = 184293.39, $p = .34$, $\eta_p^2 = .05$). The descriptive statistics and results for all the results, including time and congruency, are reported in supplemental tables 1 and 2.

We also performed a mixed ANOVA on number of errors (time x congruency x stimulation conditions) to assess whether frequency of errors changed as a function of stimulation conditions. Table 3 shows the ranges of errors by stimulation condition. None of the interaction effects with stimulation conditions were statistically significant ($F's < 2$, $p's > .3$). Thus, the number of errors was comparable for all three stimulation conditions across trials at time 1 and 2. The main effect for stimulation conditions was also not statistically

significant (F (2,45) = 0.7, MSE = 4.7, p = .51, η_p^2= .03). The congruency main effect (F (2,90) = 21.63, MSE = 2.4, p < .001, η_p^2= .33) was significant; more errors were made during incongruent trials (M = 1.92) than control trials (M = .72) and congruent trials (M = .57). All other statistical outcomes are reported in supplemental tables 1 and 2.

Unilateral stimulation

The mixed ANOVA analysis, conducted in the same manner as for the bilateral data but with stimulation conditions: right anodal/contra-supraorbital region; left anodal/contra-supraorbital region; sham, revealed a statistically significant main effect for time (F (1,30) = 70.35, MSE = 21091.87, p <.001, η_p^2= .70) with quicker performance at time 2 (M =729.39) compared to time 1 (M = 902.53). The main effect for congruency (F (2,60) = 48.35, MSE = 10648.32, p <.001, η_p^2= .62) was also statistically significant with incongruent stimuli (M = 917.91) yielding the longest latencies followed by control stimuli (M = 767.46) then congruent stimuli (M = 762.51).

The interaction effects for time and for congruency by stimulation conditions were not statistically significant (F's < 2, p's ≥ .4) nor was the 3-way interaction with time, congruency and stimulation conditions (F (4,60) = 1.88, MSE = 4853.01, p = .13, η_p^2= .11). The main effect for stimulation conditions, as with the bilateral study, was not statistically significant (F (2,30) < 1, MSE = 128168.63, p > .93, η_p^2=.01). All descriptive statistics and results for time and congruency are reported in supplemental tables 1 and 2.

The mixed ANOVA for the error data revealed that the main effect for stimulation conditions (F (2,30) = 0.68, MSE = 3.71, p = .51, η_p^2= .04) was not statistically significant. In addition, there were no statistically significant interaction effects by stimulation conditions for time or congruency (F's < 2, p's ≥.3). The 3-way interaction between time, congruency and stimulation conditions (F (4,60) = 1.37, MSE = .76, p = .26, η_p^2= .08) was also not

statistically significant. As with the bilateral study, these results indicate that the number of errors made were comparable across all the conditions irrespective of stimulation conditions. The main effect for congruency (F (2,60) = 26.07, MSE = 1.12, p < .001, η_p^2= .44) was statistically significant. We found most errors were made during incongruent trials (M = 1.55) followed by control trials (M = .70) then congruent trials (M = .32). Descriptive statistics and statistical results are reported in supplemental tables 1 and 2.

Bilateral and unilateral stimulations combined

Combining the bilateral and unilateral samples (N = 81) we conducted the same mixed ANOVA for the median data but with all 6 stimulation conditions. We found a statistically significant main effect for time (F (1,75) = 146.46, MSE= 23481.23, p < .001, η_p^2= .66) with performance at time 2 (M = 723.82) quicker than at time 1 (M = 895.02). The main effect for congruency was also significant (F (2,150) = 102.92, p < .001, η_p^2= .58). Congruent latencies were shortest followed by control trials then incongruent trials (M = 752.41< M = 762.99 <. M = 912.85, respectively).

The time and the congruency by stimulation conditions interactions and time by congruency by stimulation conditions interaction effects were not statistically significant (F's < 2, p's > .2). The main effect for stimulation conditions was also not significant (F (5,75) < 1, MSE = 161843.49, p > .74, η_p^2= .04). Descriptives and statistical results are reported in supplemental tables 1 and 2.

Error data analysis for the combined bilateral and unilateral samples (N = 81) revealed a statistically significant main effect for time (F (1,75) = 7.81, MSE = .85, p = .007, η_p^2= .09), indicating that participants made fewer errors at time 2 (M = .84) than time 1 (M = 1.08). The main effect for congruency (F (2,150) = 38.08, MSE = 1.90, p < .001, η_p^2= .34) and the interaction effect for time by congruency (F (2,150) = 9.20, MSE = .79, p <.001, η_p^2=

.11) were also statistically significant. Participants made the most errors during incongruent trials (M = 1.73), the least during congruent trials (M = .45), with control trials between the two (M = .71).

The interaction effects for time and for congruency by stimulation conditions as well as the 3-way interaction were not statistically significant (F's $\leq$ 1, p's $\geq$ .5). The main effect for stimulation conditions (F (5,75) = 0.79, MSE = 4.27, p = .6, η_p^2= . .05) was also not statistically significant. The descriptive statistics and ANOVA results are reported in supplemental tables 1 and 2.

DISCUSSION

This study aimed to assess the generalizability of Fecteau and colleagues' (2007) results on the impact of tDCS modulated activity of the DLPFC on decision-making behaviour in the BART, a task where the probability of the decision outcome is unknown. Fecteau and colleagues' results were based on a total sample of 44 participants distributed across five different stimulation conditions, including sham. Given the importance of their findings in elucidating the role of DLPFC in decision-making in ambiguous scenarios, but given the very low number of people tested, we thought it was important to assess the robustness of their finding using a much larger sample. Overall, they found that both bilateral montages used to stimulate the DLPFC yielded a *less* risk-prone response style compared to sham, while in the unilateral stimulation study there were no statistically significant effects. Conversely, in our initial bilateral study, for both outcome measures (average adjusted pumps and total money earned), we found that right anodal/left cathodal responders were *more* risk-prone than left anodal/right cathodal responders. However, importantly, neither active stimulation conditions differed significantly from sham. Given the

methodological differences between the original and our study, we conducted a second study, adhering as closely as possible, on the basis of the available information, to Fecteau et al. methodology. In this study we employed, as in the original study, both bilateral and unilateral neuromodulation protocols. We also included the classic Stroop Task as an ancillary task before and after stimulation, as in Fecteau et al.. Concordant with Fecteau et al., we found no evidence of an effect of stimulation compared to sham, which indicates that participants' selective attention was not affected by bilateral or unilateral stimulation.

In this second study, unlike Study 1 and the original study, it emerged that there was no significant effect of both bilateral and unilateral montages on the performance in the BART. Furthermore, when we combined the data from both the bilateral and the unilateral stimulation studies, it emerged that there were no significant differences among stimulation conditions. Overall then, it appears that the significant result obtained in the bilateral study was more apparent than real and that the differences in performance across stimulation montages are imputable to random variation rather than the effect of the neuromodulatory interventions. Finally, in our two studies, we had a total of 198 participants. This figure is well above 2.5 times the size of the sample in Fecteau and colleagues' study (i.e. 44), thus providing a suitable size to attempt to generalize previous findings (Simonsohn, 2015).

Given that we were unable to obtain results for the BART comparable to those obtained by Fecteau and colleagues in their bilateral stimulation montages, we will also consider the feasibility of alternative reasons other than a small sample size issue to account for the different results obtained. We used the same decision-making task as Fecteau and colleagues, which is well-validated (Lejuez et al., 2002, 2003) and has also been used in neuroimaging decision-making studies, successfully showing specific neural substrates involved in risky decision-making (e.g. Rao et al., 2008, Fukunaga et al., 2012). In addition, we replicated the positive correlation between the Sensation Seeking questionnaire output

and average adjusted pumps found by Lejuez and colleagues (2002), which suggests that participants scoring higher on sensation seeking were likely to complete more pumps (i.e. to take a greater risk). We also found that participants habituated to the task over time, taking more risks towards the end; also an effect reported in other BART studies (e.g. Lejuez et al., 2002, 2003; White et al., 2008). We are therefore fairly confident that the application of the task was appropriate. One important issue with this task, however, is that by examining only unexploded balloons some of the riskiest decisions are eliminated thereby inadvertently giving greater weight to risk-averse responses (Pleskac et al., 2008). This issue did not prevent Fecteau and colleagues from finding an effect; therefore it seems unlikely to have played a role in their between-groups comparison, though it may have impacted the strength of the effect. Overall, then our methodology, though not identical, was in principle appropriate to obtain results comparable to those of Fecteau and colleagues.

Hovarth and colleagues (2014) argued, following their review of tDCS studies, that individual differences in responding to tDCS within one sample may not re-occur in a different sample, even with the same research team, task and tDCS methodology (e.g. Fricke et al., 2011, cited in Hovarth et al., 2014). Intra-individual differences in circadian, metabolic and hormonal fluctuations are also important. Moreover, current flow is another very important issue in tDCS research. It is possible that a small amount of saline made contact with an unintended part of the scalp in some participants, creating current flow away from the area of interest. Herein lies the fundamental importance of sample size in neuromodulation studies. A certain amount of noise in the data is to be expected, however neuromodulation studies (including tDCS) typically comprise small sizes. For example, Brunoni and Fregni (2008) found in a review of clinical trials conducted with neuromodulation that 28 of 31 studies had a sample size of ≤ 68. The same is true for more recent neuromodulation studies (e.g. Wing et al., 2013; Goldman et al., 2011), one of which also used the BART in

association to transcranial alternate current stimulation (Sela, Kilim & Lavidor, 2012). We do not enter into any specific discussion of the Sela et al. (2012) study other than to point out that in the three stimulation conditions used, the total sample size was of 27 participants of whom three had later been discarded from statistical analyses due to their performance being at least two standard deviations from the mean of their condition. It is in general, unclear whether a replication of any of these studies, with a larger sample, would yield consistent results given issues such as individual differences that would have an amplified effect in a smaller sample. To this issue it is relevant to point out that another relatively large scale study using tDCS has been conducted recently to try to better understand the extent to which it may impact on a simple visual motor reaction time task by Horvath, Carter and Forte (2016). With over 200 participants tested, no significant effects were detected. On the basis of this outcome and the one obtained in the present study, we would therefore argue that neurostimulation studies should be conducted with appropriately large sample sizes to provide robust results.

CONCLUSIONS

This investigation showed that there was no detectable effect of tDCS stimulation on selective attention or risky decision-making under ambiguity. Hence, regarding the latter, we failed to generalise the results obtained previously by Fecteau and colleagues (2007) who showed that stimulating the DLPFC reduced risky decision-making compared to sham. If anything, in our bilateral stimulation study we obtained the opposite outcome. However, when the results of our bilateral and unilateral stimulation studies were considered together, it emerged that the most likely explanation for the apparent significant results in our bilateral stimulation study was random variation in performance. On this basis, and given the small sample size used by Fecteau and colleagues, the more parsimonious explanation for their, as

well as our results, is the random variation of sample means spuriously detected as statistically significant. Overall, this study is a reminder of the need of large sample studies to reliably assess the impact of tDCS neuromodulatory interventions.

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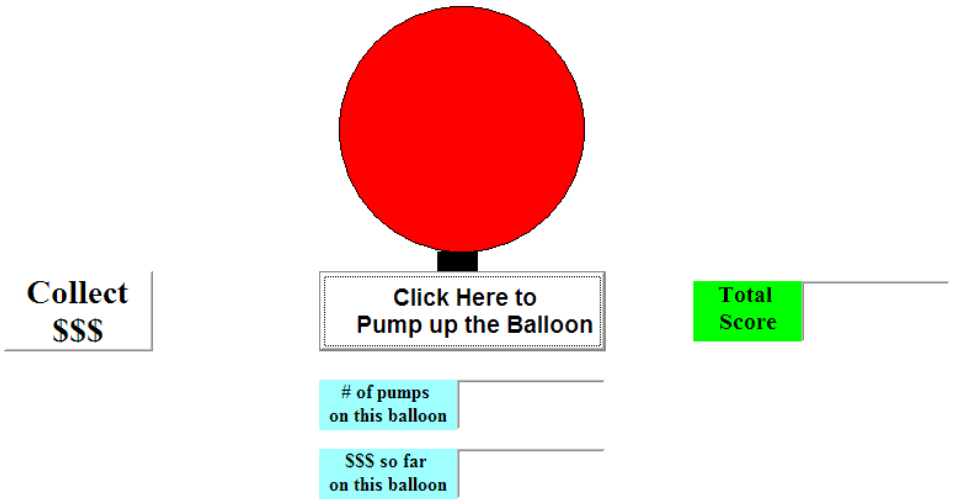


Fig. 1. The diagram shows the BART interface. Participants were asked to pump up the balloon and could stop pumping the balloon by pressing "Collect $$$" to bank what they had accumulated in their temporary bank and move on to the next balloon. Participants also knew that the balloon could explode at any time from the first pump until the balloon filled the entire computer screen. Participants knew the number of pumps ("# of pumps on this balloon"), how much money they had in their temporary bank thus far ("$$$ so far on this balloon") and the total amount in their permanent bank ("Total Score").

Fig. 2. **Diagram showing testing procedure for Study 1 (N = 117)**

Bilateral Study [n = 95]

Pre-stimulation (offline):

- Medical screening
- Informed consent
- All tasks to be administered are explained

30 min Stimulation with 2 mA* (online):

Time

Task	Duration
Comfort Visual Analogue Scale (VAS)	30 s
Watch nature video	4 min 30 s
Memory Task (memorise objects presented)	2 min
BART	10 min
Comfort VAS	30 s
Memory Recall (recall objects memorised)	2 min
IOWA Gambling Task	8 min
Comfort VAS	30 s

Post-stimulation (offline):

- Eysenck Impulsiveness Scale
- Sensation-seeking Questionnaire

**Note: For sham condition, participants received a 30 s ramp-up followed by 60 s 2 mA Stimulation followed by a 30 s ramp-down.*

Bilateral Study [n = 22]

Pre-stimulation (offline):

- Medical screening
- Informed consent
- All tasks administered are explained
- Symptom Questionnaire

30 min Stimulation with 2 mA* (online):

Time

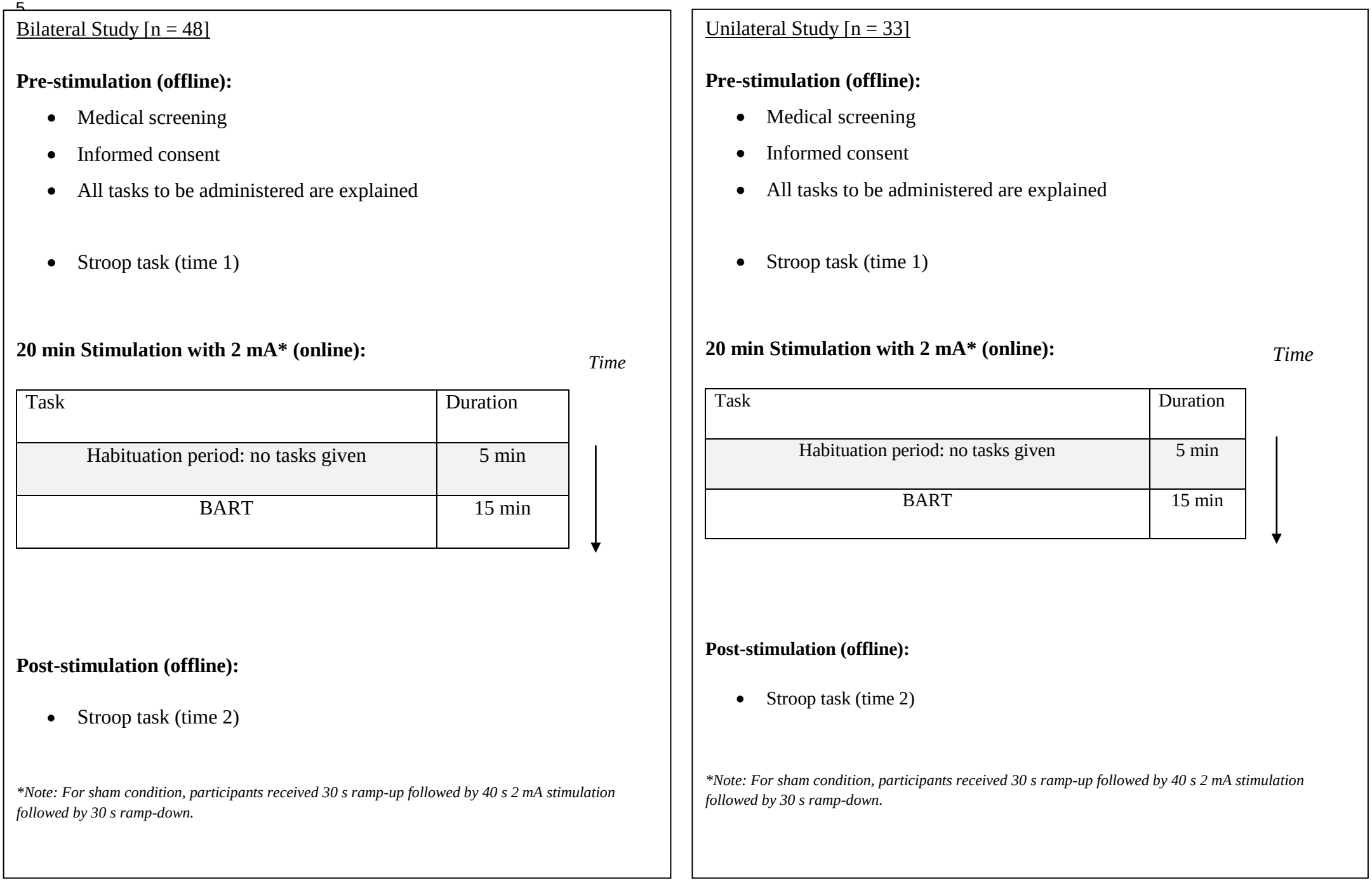
Task	Duration
Symptom Questionnaire	3 min
Watch nature video	2 min
Cambridge task	15 min
BART	10 min

Post-stimulation (offline):

- Symptom Questionnaire
- Eysenck Impulsiveness Scale
- Sensation-seeking Questionnaire
- Researcher and Participant on/off judgements

**Note: For sham condition, participants received a 30 s ramp-up followed by 60 s 2 mA Stimulation followed by a 30 s ramp-down.*

Fig. 3. Diagram showing testing procedure for Study 2 (N = 81)



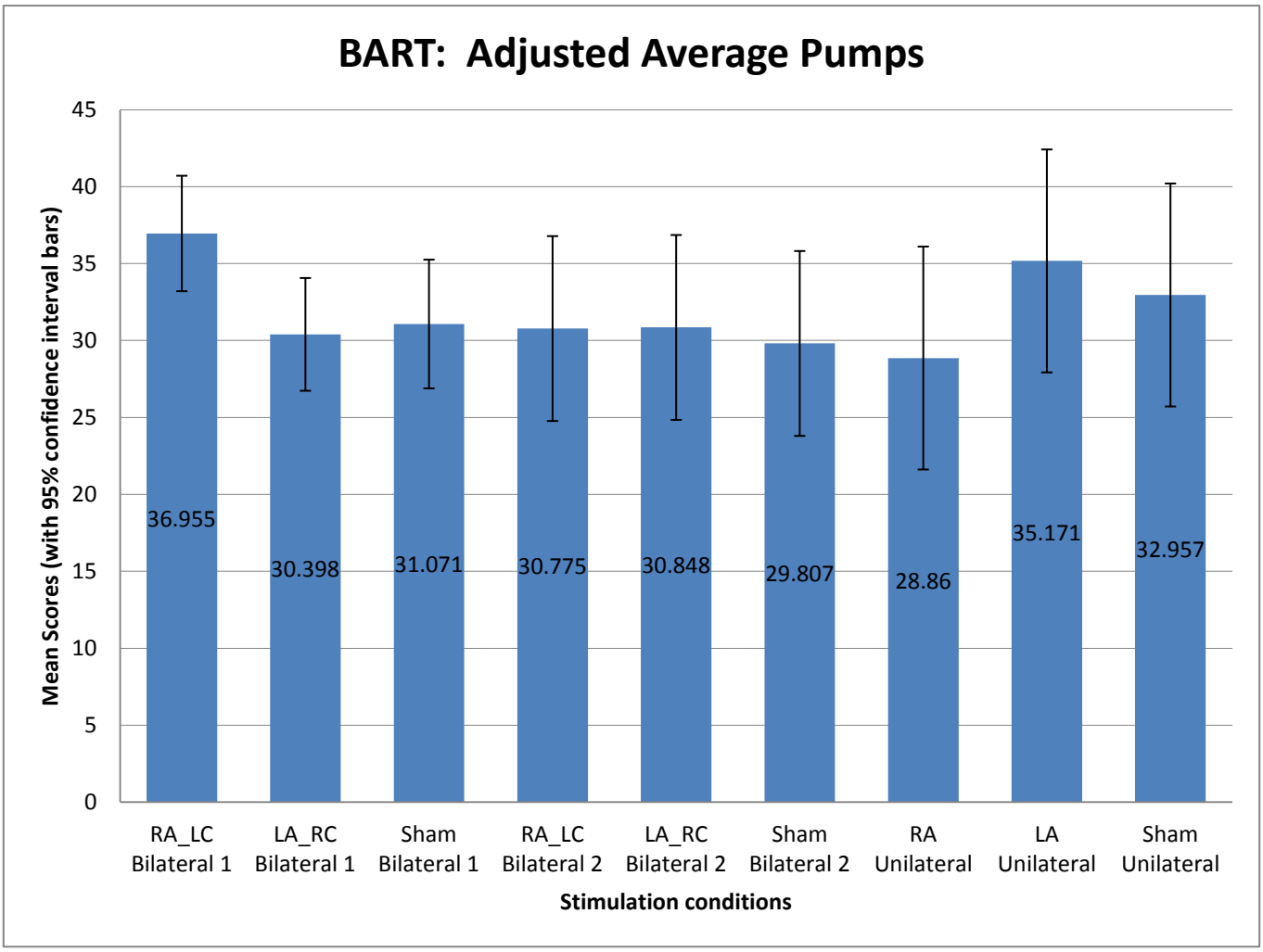


Fig. 4. Means and 95% Confidence Intervals for the average number of adjusted pumps across all stimulation conditions of Study 1 (bilateral stimulation) and Study 2 (unilateral stimulation). In order from left to right, the results are displayed by study.

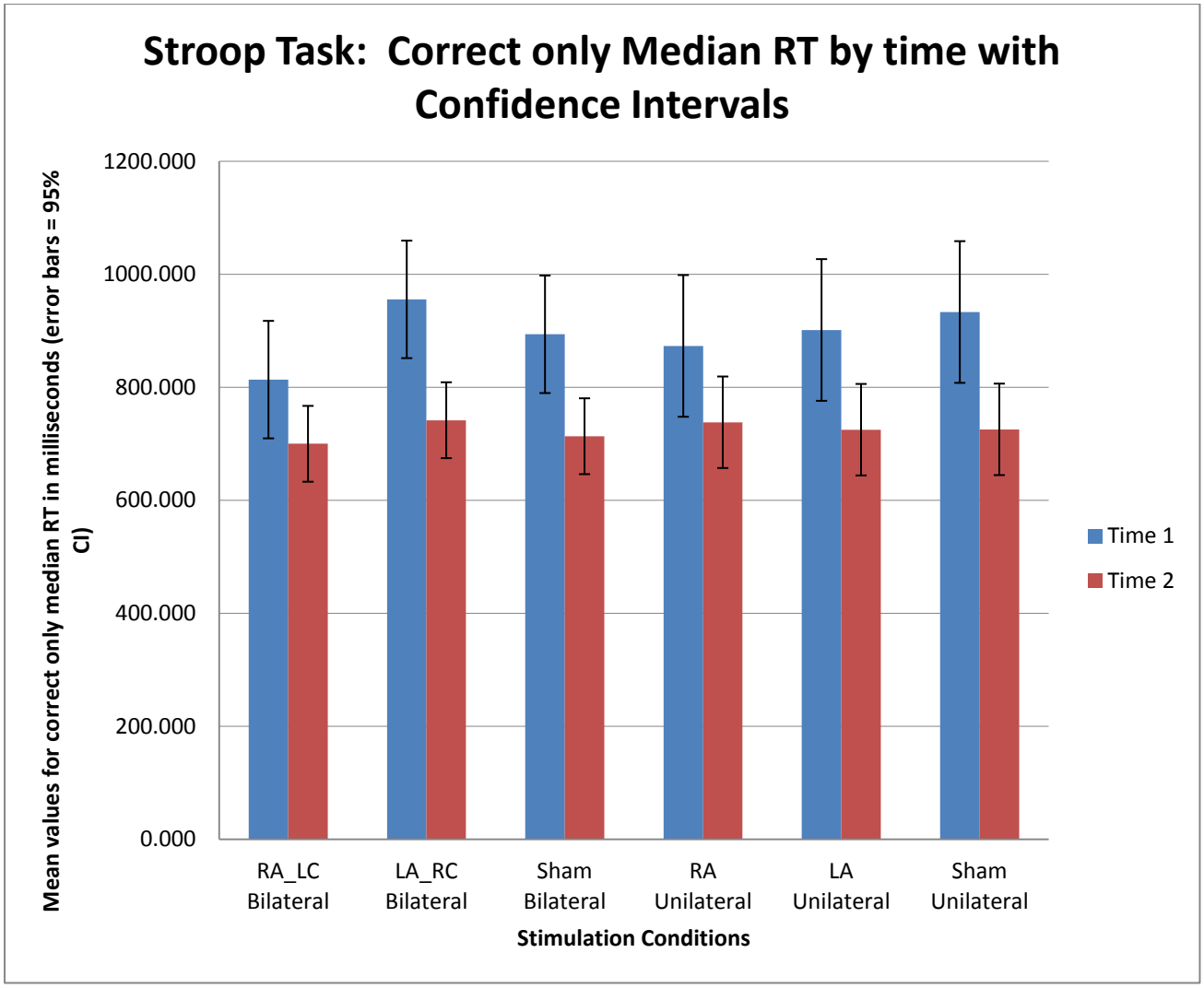


Fig. 5. Mean reaction time values and 95% Confidence Intervals for the median correct-only Stroop Task trials for all stimulation conditions of Study 2 (bilateral and unilateral stimulation). In order from left to right, the results are displayed by study.

Table 1

Study 1 and Study 2 means and standard error (SE) for the average number of adjusted pumps and money earned over time by stimulation condition.

		Average number adjusted pumps				Total Money Earned			
		1 - 10 balloons (set 1)	11 - 20 balloons (set 2)	21 - 30 balloons (set 3)	AVERAGE SCORE	1 - 10 balloons (set 1)	11 - 20 balloons (set 2)	21 - 30 balloons (set 3)	AVERAGE SCORE
	Stimulation Condition	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)
Study 1	Right Anodal/Left Cathodal (n = 41)	33.48 (1.96)	37.95 (2.15)	39.44 (2.21)	36.96 (1.95)	1,131.1 (56.2)	1,266.3 (57.4)	1,257.3 (56.6)	1,218.3 (48.1)
	Left Anodal/Right Cathodal (n = 43)	25.88 (1.91)	31.86 (2.10)	33.46 (2.16)	30.40 (1.90)	931.4 (54.8)	1,108.8 (56.1)	1,094.2 (55.2)	1,044.8 (46.7)
	Sham (n = 33)	25.12 (2.18)	32.37 (2.40)	35.73 (2.46)	31.07 (2.17)	951.2 (62.7)	1,145.0 (64.0))	1,222.4 (63.1)	1,106.2 (53.6)
Study 2 Bilateral	Right Anodal/Left Cath (n = 16)	26.53 (2.88)	32.71 (3.33)	33.09 (3.82)	30.78 (3.04)	945.0 (89.2)	1,187.2 (96.0)	1,175.0 (99.3)	1102.4 (78.7)
	Left Anodal/Right Cath (n = 16)	26.04 (2.88)	32.02 (3.33)	34.49 (3.82)	30.85 (3.04)	1021.6 (89.2)	1,084.7 (96.0)	1,212.5 (99.3)	1,106.3 (78.7)
	Sham (n = 16)	25.12 (2.88)	29.79 (3.33)	34.51 (3.82)	29.81 (3.04)	974.1 (89.2)	1,089.7 (96.0)	1,233.4 (99.3)	1,099.1 (78.7)
Study 2 Unilateral	Right Anodal (n = 11)	24.50 (3.88)	29.79 (3.79)	32.29 (3.53)	28.86 (3.35)	963.6 (114.6)	1087.7 (89.7)	1089.1 (83.1)	1046.8 (79.7)
	Left Anodal (n = 11)	31.79 (3.88)	37.94 (3.79)	35.79 (3.53)	35.17 (3.35)	1088.6 (114.6)	1,252.3 (89.7)	1,151.4 (83.1)	1,164.1 (79.7)
	Sham (n = 11)	24.04 (3.88)	36.91 (3.79)	37.92 (3.53)	32.96 (3.35)	897.8 (114.6)	1,389.6 (89.7)	1,292.3 (83.1)	1,193.2 (79.7)

Table 2.

Stroop Task median latency values (correct trials only) by Time by Congruency and Stimulation condition.

	Time 1			**Time 2**		
Stimulation Condition	Congruent Mean (SE)	Incongruent Mean (SE)	Control Mean (SE)	Congruent Mean (SE)	Incongruent Mean (SE)	Control Mean (SE)
Right Anodal/Left Cathodal Bilateral (n = 16)	767.031 (43.890)	923.656 (73.465)	749.625 (49.949)	657.219 (28.508)	776.406 (45.788)	665.906 (32.731)
Left Anodal/Right Cathodal Bilateral (n = 16)	853.750 (43.890)	1105.375 (73.465)	907.25 (49.949)	687.406 (28.508)	830.25 (45.788)	707.188 (32.731)
Sham Bilateral (n = 16)	823.156 (43.890)	1019.625 (73.465)	838.156 (49.949)	665.344 (28.508)	791.469 (45.788)	682.938 (32.731)
Right Anodal/Left Supraorbital Unilateral (n = 11)	802.727 (52.934)	1007.091 (88.602)	809.545 (60.240)	675.500 (34.382)	833.136 (55.222)	705.227 (39.475)
Left Anodal/Right Supraorbital Unilateral (n = 11)	866.682 (52.934)	984.864 (88.602)	852.455 (60.240)	662.545 (34.382)	819.545 (55.222)	692.364 (39.475)
Sham Unilateral (n = 11)	882.864 (52.934)	1075.364 (88.602)	841.136 (60.240)	684.727 (34.382)	787.455 (55.222)	704.045 (39.475)

Table 3

Stroop Task number of errors by Congruency by Stimulation condition.

	Time 1			Time 2		
Stimulation Condition	Congruent trials	Incongruent trials	Control trials	Congruent trials	Incongruent trials	Control trials
Right anodal/Left cathodal Bilateral (n = 16)	6 (0 - 3)	13 (0 - 5)	9 (0 - 2)	6 (0 - 3)	13 (0 - 5)	9 (0 - 4)
Left anodal/Right cathodal Bilateral (n = 16)	8 (0 - 2)	14 (0 - 10)	9 (0 - 5)	6 (0 - 3)	10 (0 - 7)	7 (0 - 3)
Sham Bilateral (n = 16)	4 (0 - 2)	12 (0-9)	5 (0 - 3)	4 (0 - 3)	11 (0-4)	6 (0 - 2)
Right anodal/supraorbital Unilateral (n = 11)	0	8 (0 - 5)	4 (0 - 3)	3 (0 - 2)	8 (0 - 3)	4 (0 - 3)
Left anodal/supraorbital Unilateral (n = 11)	8 (0 - 2)	9 (0 - 5)	5 (0 - 2)	3 (0 - 1)	5 (0 - 6)	4 (0 - 7)
Sham Unilateral (n = 11)	1 (0 - 1)	7 (0 - 6)	5 (0 - 2)	1 (0 - 1)	8 (0 - 3)	5 (0 - 2)

Supplementary Material

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