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*Brief Report*

# Preliminary evidence for the efficacy of single-session transcranial direct current stimulation to the ventrolateral prefrontal cortex for reducing subclinical paranoia in healthy individuals

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**Objectives.** Paranoia manifests similarly in subclinical and clinical populations and is related to distress and impairment. Previous work links paranoia to amygdala hyperactivity and reduced activation of the ventrolateral prefrontal cortex (VLPFC), a region thought to regulate amygdala activity.

**Methods.** This study aimed to reduce subclinical paranoia in 40 undergraduates by increasing activity of the VLPFC via single-session transcranial Direct Current Stimulation (tDCS). A double-blind, crossover (active vs. sham stimulation) design was used.

**Results.** Paranoia significantly decreased after active stimulation ($d_z$ = 0.51) but not sham ($d_z$ = 0.19), suggesting that tDCS of VLPFC was associated with mean-level reductions in paranoia.

**Conclusion.** These findings demonstrate preliminary support for the role of single-session active stimulation to the VLPFC for reducing subclinical paranoia in healthy individuals.

## Practitioner points

- In both clinical and subclinical populations, paranoia is related to distress and poorer functional outcomes.
- Paranoia has been linked to overactivation of the amygdala, a brain region responsible for detecting salience and threat, and reduced activation of the ventrolateral prefrontal cortex (VLPFC), a region thought to modulate and regulate amygdala activity.

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- In this study, transcranial direct current stimulation (tDCS) of the VLPFC reduced self-reported paranoia in healthy undergraduate students.
- tDCS may be a promising intervention for reducing paranoia in subclinical and clinical populations.
- Effects were relatively small and require replication with larger subclinical samples and with clinical samples.

Paranoia exists across a transdiagnostic continuum affecting those with severe mental illnesses as well as 10–28% of otherwise psychiatrically healthy individuals in the general population (Bebbington et al., 2013). The occurrence of paranoia among such healthy individuals is referred to as subclinical paranoia. A growing body of literature has begun to examine subclinical paranoia not only as it relates to clinical paranoia, but as an area of interest in its own right. Across clinical and subclinical populations, heightened paranoia is associated with poor self-esteem and elevated depression (Martin & Penn, 2001), in addition to poor physical health and psychological well-being (Rössler et al., 2007). Importantly, putatively healthy individuals who are high in subclinical paranoia experience difficulties in occupational and social functioning (Rössler et al., 2007). Due to the widespread prevalence and negative associations with heightened paranoia, effective interventions to reduce paranoia are needed.

As previous work indicates that paranoia manifests similarly in subclinical and clinical populations, it may also have similar neurological mechanisms. Previous work suggests that clinical levels of paranoia are related to overactivation of the amygdala and decreased activity in the ventrolateral prefrontal cortex (VLPFC), which typically modulates and reduces amygdala activity (Monk et al., 2008; Pinkham, Hopfinger, Ruparel, & Penn, 2008). Thus, previous work suggests that either reducing amygdala activation or increasing VLPFC activity may help to lessen paranoia (Pinkham et al., 2008). One viable option for increasing activity of the VLPFC is through transcranial direct current stimulation (tDCS), which is a novel form of neuromodulation that utilizes constant, low amplitude, direct electrical current delivered through non-invasive electrodes placed on the surface of the scalp (Brunoni et al., 2012). The easily accessible, cortical location of VLPFC renders this a better target than the subcortically located amygdala.

The purpose of the present study is to investigate whether a single session of tDCS to the VLPFC can successfully reduce subclinical paranoia in healthy individuals. We hypothesize that individuals will show reduced levels of paranoia immediately following active stimulation to the VLPFC as compared to immediately following sham stimulation. We have chosen to examine subclinical paranoia for two primary reasons. First, individuals high in subclinical paranoia experience distress and impairment despite the absence of a clinical diagnosis. tDCS may lead to reduced distress and improved outcomes for these individuals. Second, targeting a subclinical population allows for a specific test of this intervention that is unconfounded by medications or other psychotic symptoms.

## Methods

Participants included 40 undergraduate students between 18 and 35 years of age ($M$ = 20, $SD$ = 2.19) who experienced high levels of subclinical paranoia. Participants were identified from a larger sample that completed two online screening surveys including the Paranoia Scale (PS; Fenigstein & Vanable, 1992) at least one week apart ($M$ = 9.73 days, $SD$ = 4.05). The PS is a 20-item self-report measure assessing subclinical paranoia. Total score on the PS ranges from 20 to 100, with higher scores indicating greater subclinical paranoia. Individuals scoring an average of 53 or above on both

screening surveys were recruited for the current study (means are provided in Table 1). This cut-off score is consistent with previous work indicating that this is a reliable marker of elevated paranoia (Combs & Penn, 2004). The average length of time between the second PS screening assessment and the first laboratory visit was approximately 72 days (*SD* = 61.05; Median = 51 days; Range: 7–306). Participants did not meet diagnostic criteria for, or have history of, mental illness as assessed by the Mini-International Neuropsychiatric Interview (Sheehan et al., 1998) which was completed via phone screening an average of 22 days before visit 1 (Median = 17.5; *SD* = 22.89). Additionally, participants could not be taking any psychotropic medications, which was assessed during the phone screen and again during visit 1. Participant demographics and descriptive characteristics are provided in Table 1.

Testing occurred during two laboratory visits, approximately 1 week apart (*M* = 7.03, *SD* = 0.16). This study utilized a double-blind, crossover, placebo-controlled design. Participants were randomly assigned to receive either active or sham neurostimulation at their first visit and the opposite condition at their second visit. Condition assignment was counterbalanced so that approximately half of the participants received active stimulation first. Immediately before stimulation, participants completed the PS to assess current levels of paranoia (PS-pre). The assigned neurostimulation procedure was then administered for a total of 20 min, during which participants viewed the first episode of *Orbit:*

**Table 1.** Participant demographics and descriptive information

| | *M* (*SD*)/*N* (%) |
|---|---|
| Age | 20.15 (2.19) |
| Female | 25 (62.5) |
| Years of education | 13.89 (1.75) |
| Race | |
| Asian | 21 (52.5) |
| Caucasian | 16 (40) |
| African American | 1 (2.5) |
| Other | 2 (5) |
| Ethnicity | |
| Hispanic | 11 (27.5) |
| Non-Hispanic | 29 (72.5) |
| PS screening | |
| PS 1 | 60.08 (6.92) |
| PS 2 | 59.9 (5.79) |
| Sham condition | |
| PS-Pre | 47.63 (9.86) |
| PS-Post | 46.90 (10.25) |
| PS difference score (Pre – Post) | 0.73 (3.80) |
| Active condition | |
| PS-Pre | 46.58 (10.23) |
| PS-Post | 44.98 (10.02) |
| PS difference score (Pre – Post) | 1.60 (3.11) |

*Note*. PS 1 = paranoia scores during first screening; PS 2 = paranoia scores during second screening; PS difference score = paranoia scores pre-stimulation minus paranoia scores post-stimulation; PS-Post = paranoia scores post-stimulation; PS-Pre = paranoia scores pre-stimulation.

*Earth's Extraordinary Journey*. Active stimulation involved 20 min of neurostimulation at 1.5 mA using rectangular conductive rubber electrodes inside saline-soaked sponges. Given work demonstrating both anodal *and* cathodal stimulation result in excitability at durations of 20 min and at higher amplitudes (Batsikadze, Moliadze, Paulus, Kuo, & Nitsche, 2013), electrodes were placed bilaterally. To stimulate the right VLPFC, the anode was placed over F6 (Montreal Neurological Institute coordinates: 44, 32, −12 identified from Pinkham et al., 2008); the contralateral homolog area (F5) was targeted for the stimulation of the left VLPFC. Electrodes were identically placed for the sham condition; however, stimulation was limited to 45 s in total, with 15 s of gradual stimulation leading up to 15 s of full stimulation, followed by 15 s of gradual ramping down. Both electrodes were 5 × 7 centimetres in size (35 $cm^2$), resulting in a current density of 0.0428 $mA/cm^2$. Stimulation was followed by a 30-minute waiting period to allow stimulation effects to accrue and stabilize (Samani, Agboada, Jamil, Kuo, & Nitsche, 2019) during which participants browsed through magazines quietly. After the waiting period, participants completed the PS again (PS-post).

Both participants and research assistants who conducted testing were blind to study condition. Success of the blinding procedure was assessed by asking participants and researchers to guess the stimulation condition at the end of each visit. Accuracy was below chance levels (46% for participants and 48% for researchers) indicating that blinding procedures were successful. All participants provided informed consent and were compensated for their participation, and all participants completed both visits.

## Results

A repeated-measures ANOVA on PS scores, with condition (active vs. sham) and time (pre- vs. post-stimulation) as within-subjects variables, was used to test whether VLPFC stimulation reduced paranoia. This revealed a significant main effect of condition, $F(1, 39) = 4.407$, $p = .042$ such that paranoia was lower in the active condition ($M = 45.78$, $SD = 9.99$) relative to sham ($M = 47.26$, $SD = 9.87$). The main effect of time was also significant, $F(1, 39) = 9.865$, $p = .003$, with lower PS scores in the post-stimulation assessments ($M = 45.94$, $SD = 9.80$), relative to pre-stimulation ($M = 47.10$, $SD = 9.74$). The interaction between condition and time on paranoia was not significant, $F(1, 39) = 1.16$, $p = .29$.

Follow-up paired samples $t$ tests between pre- and post-PS scores for the active and sham conditions revealed a statistically significant decrease in PS scores for the active condition, $t(39) = 3.25$, $p = .002$ but not sham, $t(39) = 1.21$, $p = 0.24$. Further, effect size calculations revealed a larger effect size in the active condition ($d_z = 0.51$) than sham ($d_z = 0.19$). These results provide preliminary support for the conclusion that active tDCS to the VLPFC is associated with decreases in subclinical paranoia.

## Discussion

The current study tested whether single-session stimulation of VLPFC, a neural region known to modulate amygdala activity, would result in decreased paranoia in healthy individuals. While results were somewhat modest, paranoia decreased significantly following active stimulation and not following sham stimulation. Thus, this provides preliminary evidence that tDCS to the VLPFC may be a viable treatment for reducing paranoia in subclinical populations. Given that tDCS appears to improve negative

symptoms (Aleman, Enriquez-Geppert, Knegtering, & Dlabac-de Lange, 2018) and hallucinations (Yang et al., 2019) in schizophrenia, it is also possible that the current results would extend to clinical levels of paranoia as well, though future investigations are needed.

The current findings require replication with larger samples, additional measures of paranoia and assessment of potentially related states such as depression and anxiety. Methodological changes should also be tested. Specifically, while an effect was found here using only a single stimulation, repeated stimulation may produce more robust results (Kim et al., 2019). The optimal lag between stimulation and testing has also been called into question (for a review, see Kostova, Cecere, Thut, & Uhlhaas, 2020), and it is possible that testing either during, or immediately after, stimulation may have resulted in more pronounced findings. The optimum duration and dose of stimulation are also currently unclear (Brunoni et al., 2012), as is the full mechanism of tDCS to the VLPFC. Since we were aiming to reduce activity of the amygdala, a deep brain structure, by stimulating its regulatory region (VLPFC), it is necessary to utilize functional neuroimaging to ensure our proposed mechanism is working as predicted. Finally, PS scores at stimulation visits remained elevated relative to normative data (Fenigstein & Vanable, 1992), but were somewhat lower than those obtained at screening. Replicating the study with healthy individuals endorsing even more paranoia would extend the current findings to the fuller spectrum of subclinical paranoia.

Despite these considerations, this study is the first to specifically target paranoia via tDCS. We observed moderate reductions in paranoia following active stimulation to the VLPFC suggesting that tDCS offers promise as a treatment for paranoia. The current results also provide tentative, indirect support for the proposed interactions between VLPFC and amygdala as a mechanism for paranoia. Continued investigation with both subclinical and clinical samples is warranted.

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## Conflicts of interest

All authors declare no conflict of interest.

## Author contributions

Cassi R. Springfield (Data curation; Formal analysis; Investigation; Project administration; Writing – original draft; Writing – review & editing) Rabab S. Isa (Data curation; Formal analysis; Investigation; Writing – original draft; Writing – review & editing) Emily L. Bass (Data curation; Investigation; Project administration; Writing – review & editing) Amy Pinkham (Conceptualization; Data curation; Formal analysis; Methodology; Project administration; Resources; Supervision; Validation; Writing – review & editing) Sven Vanneste (Conceptualization; Methodology; Resources; Supervision; Writing – review & editing).

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