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The impact of targeted cathodal transcranial direct current stimulation on reward circuitry and affect in Bipolar Disorder

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Abstract

Bipolar Disorder is costly and debilitating, and many treatments have side effects. Transcranial Direct Current Stimulation (tDCS) is a well-tolerated neuromodulation technique that may be a useful treatment for Bipolar Disorder if targeted to neural regions implicated in the disorder. One potential region is the left ventrolateral prefrontal cortex (vlPFC), which shows abnormally elevated activity during reward expectancy in individuals with Bipolar Disorder. We used a counterbalanced repeated-measures design to assess the impact of cathodal (inhibitory) tDCS over the left vlPFC on reward circuitry activity, functional connectivity, and affect in adults with Bipolar Disorder, as a step toward developing novel interventions for individuals with the disorder. −1mA cathodal tDCS was administered over the left vlPFC versus a control region, left somatosensory cortex, concurrently with neuroimaging. Affect was assessed pre and post scan in remitted Bipolar Disorder(n=27) and age/gender-matched healthy (n=31) adults. Relative to cathodal tDCS over the left somatosensory cortex, cathodal tDCS over the left vlPFC lowered reward expectancy-related left ventral striatal activity ($F(1,51)=9.61, p=.003$), and was associated with lower negative affect post scan, controlling for pre-scan negative affect, ($F(1,49)=5.57, p=.02$) in all participants. Acute cathodal tDCS over the left vlPFC relative to the left somatosensory

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Author contributions

M.A.B., H.W.C., and M.L.P. completed the literature search; M.A.B., B.A.C., E.K.E., and M.L.P. created the figures; H.W.C., B.D.G., and M.L.P. designed the study; H.W.C., S.G., R.S. collected the data; M.A.B., H.W.C., and R.S. performed data analysis; M.A.B., H.W.C., B.A.C., B.D.G., and M.L.P. data interpretation; M.A.B., H.W.C., B.A.C, B.D.G., and M.L.P. writing the manuscript.

Conflict of Interest

M.A.B., H.W.C., S.G., R.S., E.K.E., B.A.C., B.D.G., and M.L.P. have no financial interests or potential conflicts of interest. The study sponsors had no role in study design, data collection, analysis, interpretation of data, trial design, patient recruitment, or any aspect pertinent to the study; sponsors were also not involved in the writing of the report or in the decision to submit the paper for publication. The corresponding author had full access to all data in the study and the final responsibility for the decision to submit for publication.

Data Sharing

Individual data along with a data dictionary defining each field are available at the NIMH data archive repository, updates made every six months to study end, https://data-archive.nimh.nih.gov/. Following data use certification scientists can access these data.

Ethical Standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

cortex reduces reward expectancy-related activity and negative affect post tDCS. Building on these findings, future studies can determine whether chronic cathodal tDCS over the left vlPFC has sustained effects on mood in individuals with Bipolar Disorder, to guide new treatment developments for the disorder.

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Introduction

Bipolar Disorder is the fourth leading cause of disability worldwide[1]. Unfortunately, many treatments have long-term side effects. The development of new interventions for Bipolar Disorder is critical. One way forward is to identify neural biomarkers of underlying pathophysiologic processes that can act as targets for interventions. Individuals with or at-risk for Bipolar Disorder show elevated reward sensitivity[2], associated with a more severe course[3], impulsivity[4], sensation seeking[3], and high levels of reward expectancy, predisposing to hypo/mania[4], a pathognomonic feature of Bipolar Disorder. Reward expectancy involves subjective evaluation of potential future rewards, with more probable rewards having greater expected value. Undue focus on such rewards in individuals with, and at-risk of developing, Bipolar Disorder during reward expectancy may predispose to hypo/mania[4]. Determining the neural basis of subjective evaluation of future rewards during reward expectancy is thus a promising way to elucidate neural mechanisms predisposing to hypo/mania. We reported an abnormally steep increase in left reward expectancy-related ventrolateral prefrontal cortex (vlPFC) activity with greater probability of reward in euthymic Bipolar Disorder adults[5]. Other studies reported greater reward expectancy-related activity in left lateral prefrontal cortex and ventral striatum (VS) in adults with high versus low impulsivity[6] or reward sensitivity[7]. Furthermore, abnormally elevated reward-related left vlPFC activity in healthy youth at risk of Bipolar Disorder[8], manic individuals[9], and adults with higher levels of sensation seeking and impulsivity[10], who are at higher risk of Bipolar Disorder than the general population[2], have been reported.

The left vlPFC encodes relationships between stimuli and specific reward outcomes[11], particularly immediate future rewards[12]. This lateralization of stimulus-outcome representations in vlPFC function likely reflects role of the left frontal cortex in approach behaviors[13]. Other regions important for reward processing are: VS, orbitofrontal cortex (OFC), dorsal and rostral anterior cingulate cortex (d/rACC), and amygdala. The VS receives inputs from the OFC, is involved in goal directed behaviors[14] and processes the incentive value of expected reward/loss[15]. The d/rACC support responses to obtain reward[15]. Greater dACC activity in particular reflects preferences for higher probability reward options[16]. The critical interactions between VS and amygdala for reward and punishment indicate the amygdala's important role in reward processing[17]. These regions are thus important for reward valuation during RE, where abnormally elevated left vlPFC activity and functional connectivity (FC) with other reward regions in individuals with Bipolar Disorder likely reflects greater valuation of potential rewards, predisposing to hypo/mania. Hence, the left vlPFC may be a viable neural target for new interventions for the disorder.

Transcranial direct current stimulation (tDCS) involves passing a weak current through the brain to modulate endogenous electric fields produced by transmembrane currents[18]. Anodal (excitatory) tDCS results in subthreshold depolarization of cortical pyramidal cells, increasing neuronal excitability and leading to increased neuronal-neuronal connectivity[19]. Cathodal (inhibitory) tDCS results in hyperpolarization, decreasing neuronal excitability and leading to reduced connectivity[19]. As the magnitude of de/hyperpolarization imposed by tDCS is quite small, the effects of stimulation are dependent on endogenous currents as well. Thus, tDCS is thought to preferentially modulate neural networks with heightened activity during task performance- the "activity-selectivity" hypothesis[20].

Prior studies have used tDCS to treat psychiatric disorders, including Bipolar Disorder, and report that it is well tolerated[21]. Importantly, in an early tDCS trial applying anodal tDCS over the left lateral prefrontal cortex in depressed individuals with Major Depressive Disorder or Bipolar II Disorder [22], one Bipolar II Disorder individual developed hypomania[23]. Notably, the electrode montage used provided relatively high-amperage *anodal* (.08-.15V/m) tDCS to the left vlPFC[24]. Another case report showed that tDCS over the left lateral prefrontal cortex was associated with the development of hypomania in individuals with Bipolar II Disorder[25]. Thus, anodal tDCS over the left vlPFC may be associated with elevated activity in, and/or functional connectivity with, this region, and development of hypomania in individuals with Bipolar Disorder. Non-clinical studies reported altered lateral prefrontal cortex activity and functional connectivity in reward circuitry during task performance in healthy adults after tDCS over lateral prefrontal cortical regions[26]. Additionally, anodal tDCS over the right vlPFC reduces negative affect in healthy individuals[27]. Together, these findings indicate that tDCS can modulate activity in reward circuitry regions, and affect, and may be a potential intervention for Bipolar Disorder.

Given our findings of abnormally elevated reward expectancy-related left vlPFC activity in euthymic individuals with Bipolar Disorder[5], we aimed to determine whether acute cathodal tDCS over the left vlPFC would impact affect and reward expectancy-related left vlPFC activity and functional connectivity with other reward regions in remitted Bipolar Disorder and healthy individuals. We recruited Bipolar Disorder individuals in remission in order to focus on predisposition to, rather than present, hypo/mania, and avoid any potential confounds of higher severity affective symptoms and related higher levels of psychotropic medication on the impact of tDCS in individuals with Bipolar Disorder in this first-stage, proof of concept study. Given the activity-selectivity hypothesis, we administered tDCS during the reward task, while measuring BOLD fMRI. We hypothesized that acute cathodal tDCS over the left vlPFC versus over a control neural region (control condition tDCS) would: 1. significantly reduce activity and functional connectivity in reward circuitry; and 2. significantly lower positive and hypo/mania-related negative affect. We further hypothesized that these effects would be of greater magnitude in Bipolar Disorder versus healthy participants, given the likely higher levels of these measures in Bipolar Disorder than healthy participants during control condition tDCS.

Methods

Participants

We recruited adults with Bipolar Disorder type-I (remitted:≥2 months euthymic and not psychotic). 27 adults with Bipolar Disorder and 31 age and gender ratio-matched healthy adults were included (mean age= (28.5), SD= (7.16), 36 female; Table1; Supplement Figure1 for recruitment stream, Supplement for clinical measures, exclusion criteria, and numbers of included and excluded participants). 18 Bipolar Disorder participants were taking one or more mood stabilizers, 3 were taking antipsychotic medication, 5 an antidepressant, 5 benzodiazepines, and 1 was taking propranolol.

The University of Pittsburgh Institutional Review Board approved this study, and participant consent was acquired. See Figure 1 for the study design.

Reward task

Participants completed two, 8-minute blocks of an event-related card-guessing game examining neural activity during expectancy and receipt of reward/loss, comprising 96 trials, including 12 possible win, 12 possible loss, 12 possible win/loss trials (either win or loss), or 12 neutral condition in each of the two blocks. All 4 trial types were used to compute the reward expectancy regressor. Trials were presented in pseudorandom order. Participants believed that their performances determined outcome, with $1 for winning and 75¢ deducted for losing. The outcome of each trial was however, predetermined, with $6 won (Supplement).

tDCS procedure

Concurrent with the reward task during fMRI a constant −1mA current was administered using the Neuroelectrics Starstim tCS system via saline-soaked sponge electrodes and non-ferromagnetic wires (www.neuroelectrics.com Barcelona, Spain). −1mA current was used, as this is sufficient to produce neural inhibition beneath the cathode[28] while avoiding paradoxical excitation observed with higher current[29]. The cathode was positioned at the F7 EEG electrode location (10-10 system, over left vlPFC). The anode was extracephalic (EC), placed on the contralateral shoulder, as in previous tDCS studies[22]. Electrodes and sponges were circular (5.8cm diameter). tDCS was administered during the reward task (duration 16.5 minutes), with 30 seconds ramp up at the start, and 30 seconds ramp down at the end of the task: total time 17.5 minutes.

Participants completed two scans in counterbalanced order approximately one week (interscan interval =6.8 days 1.1 SD) apart: one scan was with F7-EC montage targeting the left vlPFC as described above; and the other scan was with CP1-EC montage targeting the left somatosensory cortex. Participants were blind to montage order. (See Supplement for montage order assignment methods). The left somatosensory cortex was chosen as the control region, as somatosensory cortex tDCS has minimal influence on vlPFC and subcortical regions[30]. Neurotargeting (SIMnIBS:simnibs.org and ROAST, version 2.7, http://www.parralab.org/roast/; Supplement) confirmed that cathodal tDCS over the left vlPFC resulted in a more focal and higher magnitude electric field at (and current flow to) the

left vlPFC than did cathodal tDCS over the left somatosensory cortex (Figures 2A, B and Supplement Figures 2-8)[31]. The order of the two scans was counterbalanced across participants in each group to avoid conflation of montage type with any potential practice effects over the two scans on neural and behavioral measures of interest.

Affect

Affect was assessed using the Positive and Negative Affect Schedule (PANAS)[32] immediately before and after each scan.

Data processing

Please see Supplement for data preprocessing and processing. Three primary neural regions were: left vlPFC (mni:−45 26 −8, k=344), constructed using activation likelihood estimation (ALE) (Supplement), and left and right VS (8mm sphere ±9, 9, −8)[33], constructed using the WFU PickAtlas (Wake Forest University, USA)[34]. Secondary neural regions were: Pickatlas-Brodmann Area-defined right and left amygdala, d/rACC (BA32,24), and OFC (BA11). Left vlPFC functional connectivity was measured using Generalized Psychophysiological Interaction (gPPI)[35], with primary targets: left and right VS, and secondary targets: left and right amygdala, d/rACC, and OFC. At the second level whole region eigenvariate parameter estimates were extracted using SPM12 (Table 2).

Statistical analysis methods

Analysis of the impact of tDCS on neural measures—Please see Supplement for power calculation and assumption tests. Given that recruitment of the matched participants in this study was from the community and participants were not hierarchically related, repeated measures ANOVAs were used. We tested the effect of tDCS montage (tDCS over left vlPFC versus left somatosensory cortex), group (Bipolar Disorder versus healthy), and tDCS montage×group interaction, on primary and secondary neural regional reward expectancy-related activity and functional connectivity (left vlPFC seed), accounting for age, gender, IQ, and counterbalance order. Repeated measures ANOVA is similar to one-way ANOVA with the ability to test non-independent within subjects' effects. False Discovery Rate (FDR) was used to correct for parallel ANOVAs (p-value=0.01) [36]. We used IBM Statistics SPSS 24 [37] and report degrees of freedom, test statistics, and p-values for each repeated measures ANOVA.

Analysis of the impact of tDCS on post-scan affect—Two repeated measures ANOVAs, accounting for pre-scan affect, age, gender, IQ, and counterbalanced order, examined the effect of tDCS montage, group, and tDCS montageXgroup interaction on post-scan positive and negative affect, (FDR correction, p=.04)[36]. Using regularized regression, to model the large number of predictor variables (p=24)[38] (Supplement), we then identified predictors of post-scan affect, including the above demographic, clinical, and neural measures, accounting for pre-scan affect. We report non-zero coefficients identified in this model, and parameters from standard regression analyses showing the association strengths.

Additional analyses—*T-tests* examined relationships between medication, symptom severity, and neural measures with each tDCS montage in participants with Bipolar Disorder(Supplement). To test the specificity of tDCS effects on neural measures to RE, similar analyses were performed using neural measures to reward-related prediction error and ANOVAs (FDR-corrected threshold, p=0.01; Supplement). For t-tests and reward related prediction error repeated measures ANOVA we report degrees of freedom, test statistics, and p-values.

Results

Effect of tDCS on primary neural measures

There was a main effect of tDCS montage on reward expectancy-related left VS activity (F(1,51)=9.61,p=.003), with lower activity during cathodal tDCS over the left vlPFC than left somatosensory cortex in all participants (Table2, Figure3A). There was no effect of montage on any other primary neural measures; and no effects of group, montage×group interaction, age, gender, or counterbalance order on primary neural measures (Table2).

Effect of tDCS on secondary neural measures

There was a main effect of tDCS montage on reward expectancy-related activity in left BA 24 (F(1,51)=7.15,p=.01); right BA24 (F(1,51)=8.24,p=.006); and left BA32 (F(1,51)=8.58,p=.005): activity in these regions was lower with cathodal tDCS over the left vlPFC than over the left somatosensory cortex; and a group by tDCS montage interaction (F(1,51)=8.86,p=.004) on reward expectancy-related right amygdala activity, with greater activity with cathodal tDCS over the left vlPFC than over the left somatosensory cortex in Bipolar Disorder, and lower activity with cathodal tDCS over the left vlPFC than over the left somatosensory cortex in healthy, participants (Table2, Supplement Figure 9). These findings were primarily driven by montage effects in healthy participants (Supplement Figure 9). There were no other significant effects of montage, group, or montage×group interaction.

Effect of tDCS on post-scan affect

Pre-scan negative affect did not differ significantly across groups for left vlPFC (t(56)=−.87, p=.390) and left somatosensory cortex tDCS (t(56)=−.80,p=.428). Negative affect was lower post versus pre-scan in all participants for each montage. For post-scan negative affect, controlling for pre-scan negative affect, age, gender, IQ, and counterbalance order, there was a main effect of montage (F(1,49)=5.57,p=.02), with lower negative affect after cathodal tDCS over the left vlPFC than over the left somatosensory cortex (Figure3B). PANAS negative affect descriptions that were strongly correlated with total negative affect scores and impacted by cathodal tDCS over the left vlPFC were: irritable, distressed, upset, scared, nervous, jittery, and afraid (all rs>.696). There was no effect of group (F(1,49)=.31,p=.579) or tDCS montageXgroup interaction (F(1,49)=1.04,p=.313) on post-scan negative affect. There was no effect of montage (F(1,49)=2.44,p=.124), group (F(1,49)=2.87,p=.097), or tDCS montageXgroup interaction (F(1,49=.83,p=.367) on post-scan positive affect, controlling for pre-scan positive affect, age, gender, IQ, and counterbalance order.

Predictors of post-scan affect after tDCS over left vlPFC and left somatosensory cortex

As there was no effect of tDCS montage on post-scan positive affect (above), analyses focused on identifying predictors of post-scan negative affect. Across all participants, lower negative affect after cathodal tDCS over the left vlPFC, controlling for pre-scan negative affect, was predicted by lower left vlPFC activity during cathodal tDCS over the left vlPFC (exp coeff=2.248), lower pre-scan negative affect (exp coeff=.0705), and having cathodal tDCS over the left vlPFC on the second (exp coeff=−.686). Standard regression analysis showed that following cathodal tDCS over the left vlPFC, these three variables explained 21.8% of the variance in post-scan negative affect ($F(3,54)=45.12, p=.004$), with left vlPFC activity $t=2.38, p=.021$ alone explaining 8.2% (more than 1/3 of the variance; Figure3C). Following cathodal tDCS over the left somatosensory cortex, only pre-scan negative affect (exp coeff=.446) and age (exp coeff= −.0427) were non-zero predictors of post-scan negative affect ($F(1,54)=21.34, p<.001$).

*Relationships with medicatio*n

There were no significant relationships between psychotropic medication use (taking/not taking) and reward expectancy-related neural measures during cathodal tDCS over either the left vlPFC or the left somatosensory cortex (all ps > .059).

Discussion

We aimed to determine whether acute cathodal tDCS over the left vlPFC impacted reward expectancy-related activity and functional connectivity in reward circuitry, and affect, in Bipolar Disorder and healthy adults. We show for the first time that acute cathodal tDCS over the left vlPFC relative to over the left somatosensory cortex significantly reduced reward expectancy-related bilateral VS activity. Furthermore, negative affect was significantly lower after cathodal tDCS over the left vlPFC than over the left somatosensory cortex, after controlling for pre-scan negative affect; and lower post-scan negative affect was associated with lower reward expectancy-related left vlPFC activity during cathodal tDCS over the left vlPFC, but not left somatosensory cortex.

There is uncertainty about the efficacy of tDCS because some electrode montages disperse current throughout the cortex rather than targeting neural circuitry of interest[20]. Our findings indicate, however, that cathodal tDCS significantly impacted primary and secondary neural measures when targeted over the left vlPFC versus the left somatosensory cortex. Our findings thus add to the increasing literature indicating focal effects of cathodal tDCS on reward circuitry[26]. Interestingly, there were no effects of cathodal tDCS over the left vlPFC on reward expectancy-related left vlPFC activity as measured by BOLD fMRI; instead, effects were on activity in connected regions, including left VS, and bilateral rACC, dACC and amygdala. These findings are consistent with other studies showing effects of tDCS on regions downstream from stimulated cortical areas[39].

All effects of cathodal tDCS over left vlPFC versus left somatosensory cortex were on primary and secondary neural measures to reward expectancy, with no significant findings to reward-related prediction error (Supplement and Supplement Table 1). One

explanation for these reward expectancy-specific findings relates to the activity-selectivity hypothesis, where tDCS is thought to preferentially modulate neural networks with heightened activity, e.g., during task performance, rather than at rest[20]. Indeed, whole-brain analyses (Supplement Tables2-4) revealed that, while both Bipolar Disorder and healthy participants showed significantly greater activity to reward related prediction error than reward expectancy in right VS during the control tDCS condition, as predicted by previous studies showing VS activity to reward related prediction error [10], both groups showed significantly greater reward expectancy- than reward related prediction error-related left vlPFC functional connectivity across the brain during control tDCS. Thus, the greater impact on primary and secondary neural measures of cathodal tDCS over left vlPFC during reward expectancy than during reward related prediction error might have resulted from participants showing significantly greater left vlPFC-reward circuitry functional connectivity to reward expectancy than reward related prediction error, as is evident for patterns of functional connectivity during the control tDCS condition.

All participants demonstrated significantly lower post-scan negative affect after cathodal tDCS over the left vlPFC versus the left somatosensory cortex, controlling for pre-scan negative affect. Furthermore, there was a significant positive association between post-scan negative affect after, and reward expectancy-related left vlPFC activity during, cathodal tDCS over the left vlPFC. While reward expectancy-related left vlPFC activity was not significantly different during cathodal tDCS over the left vlPFC versus left somatosensory cortex, the specificity of the relationship between lower post-scan negative affect after, and reward expectancy-related left vlPFC activity during, cathodal tDCS over the left vlPFC suggests that there may have been a more subtle impact of cathodal tDCS over left vlPFC on reward expectancy-related left vlPFC activity, where lower left vlPFC activity resulted in lower negative affect post tDCS. The reduction in negative affect included descriptive components associated with hypo/mania and depression, e.g., irritable, distressed, upset, rather than descriptions associated primarily with depression, e.g., guilt and shame. These indicate an impact of cathodal tDCS over the left vlPFC predominantly on affective components relating to arousal and irritability, characterizing hypo/mania rather than depression. Post-scan positive affect was not differentially affected by the two montages, suggesting that cathodal tDCS over the left vlPFC impacted negative, but not positive, hypo/mania-related affect. This finding may reflect the role of the left vlPFC in impulsive decision-making, associated impatience, and negative affect, when unable to delay gratification[4].

The overall findings regarding the impact of cathodal tDCS over the left vlPFC on neural measures and affect were similar in Bipolar Disorder and healthy participants, possibly reflecting the remission status of Bipolar Disorder participants, and suggesting a perturbation of the physiological relationships between neural and affective measures in all participants by cathodal tDCS over this region. The impact of tDCS over the left vlPFC may be greater in participants with Bipolar Disorder in hypo/manic or mixed mood episode, given higher levels of arousal and irritability, and likely associated reward circuity reward expectancy-related activity and functional connectivity in the latter. The effect of montage was more pronounced on primary than secondary neural measures in participants with Bipolar Disorder, however, and one secondary measure, reward expectancy-related

right amygdala activity, was not lower during cathodal tDCS over left vlPFC versus left somatosensory cortex in these participants. The relative absence of effects on secondary neural measures in participants with Bipolar Disorder may result from aberrant connectivity between left vlPFC and secondary neural regions (rACC, dACC, amygdala) implicated in reward and emotional regulation in these participants[14]. Together with the effects of cathodal tDCS over left vlPFC on negative affect, these findings highlight a need for future clinical trials of cathodal tDCS over left vlPFC in Bipolar Disorder, informed by a mechanistic understanding of neural circuity-affect relationships in Bipolar Disorder in the present proof of concept study. Having cathodal tDCS over left vlPFC on the second scan was a predictor of lower negative affect post cathodal tDCS over left vlPFC. Although difficult to explain, this finding may suggest that effects on negative affect were more apparent after repeated tDCS and may call for the use of multi-session tDCS in future clinical trials.

The absence of a sham tDCS condition could be seen as a limitation here; however, previous studies indicate that participants can often distinguish between actual and sham tDCS[40]. Furthermore, given our specific hypothesis regarding the left vlPFC, it was important to include a tDCS condition that controlled for the general impact of cathodal tDCS over the left hemisphere. The placement of the left vlPFC electrode was determined using a tight-fitting cap with a 5.8cm electrode. While there is a possibility that the electrode shifted during scanning, this was unlikely due to the rigid cap and chin strap employed, which ensured that the cap and electrode remained fixed in their original positions. Although we did not include a non-tDCS baseline scan because of participant burden, this can be included in future studies. We employed conventional rather than high definition (HD) montages to target the left vlPFC and left somatosensory cortex. While the latter are thought to have more focal effects on neural circuity of interest [20], neurotargeting showed a more focal and higher magnitude electric field at the left vlPFC by cathodal tDCS over the left vlPFC than over the left somatosensory cortex. These findings thus suggest that the montages we employed produced the hypothesized effects on neural circuitry of interest. While studies employed higher currents, we chose −1mA, as there are paradoxical excitatory effects of higher-dose cathodal tDCS[29]. Additionally, using techniques such as EEG can provide more fine-grained examination of the impact of targeted cathodal tDCS on connectivity measures such as coherence among regions of interest in reward circuitry. A more nuanced affect measure may add variance and facilitate detection of between-group differences regarding the impact of tDCS on affect in Bipolar Disorder and healthy participants. Many Bipolar Disorder participants were taking psychotropic medications, but these did not impact neural measures (Supplement).

Conclusion

We show for the first time that acute cathodal tDCS over the left vlPFC, relative to acute cathodal tDCS over a control region, significantly reduces reward expectancy-related reward circuitry activity and is associated with lower post tDCS negative affect in remitted Bipolar Disorder and healthy participants. We show proof of concept for the potential use of cathodal tDCS over the left vlPFC as an intervention for Bipolar Disorder. Building on this concept, future studies can determine the extent to which chronic administration of cathodal tDCS over the left vlPFC has sustained effects on mood in hypo/manic individuals

with Bipolar Disorder, to prepare for randomized clinical trials examining the efficacy of this intervention in the disorder.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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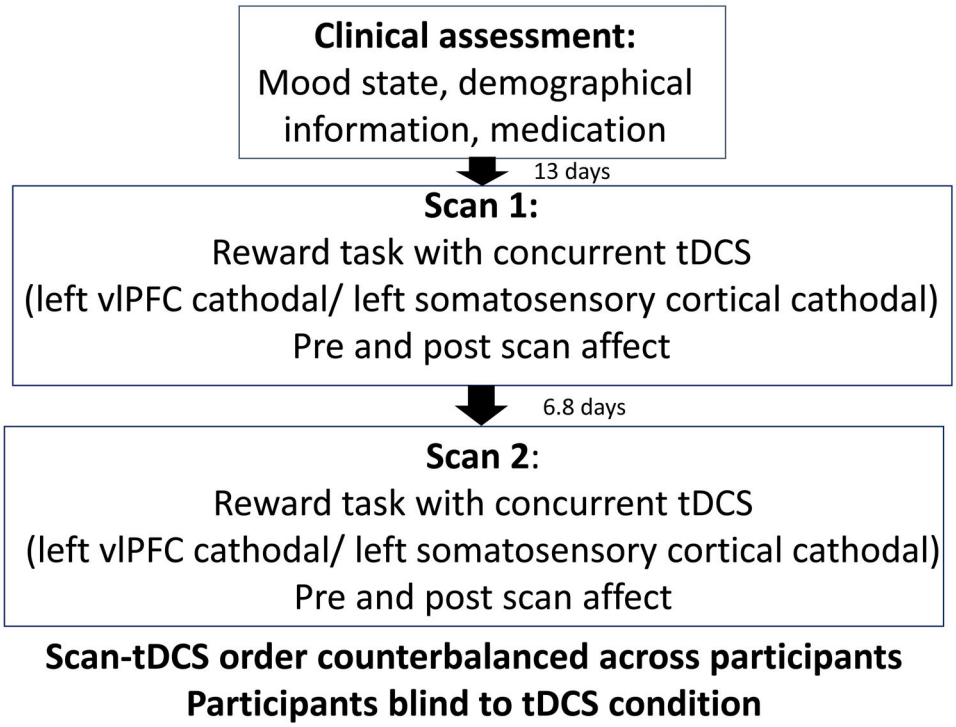

Figure 1.
Study design

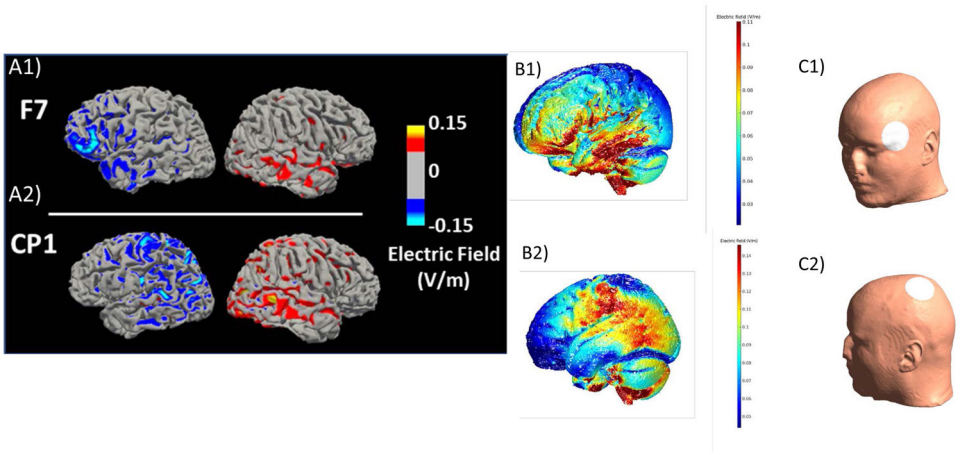

Figure 2.

Electric (E)field modeling using two software packages, (A) Simulation of Non-Invasive Brain Stimulation (SimNIBS) http://www.simnibs.org/ and (B) Realistic vOlumetric Approach to Stimulate Transcranial Electric Stimulation (ROAST, version 2.7, http://www.parralab.org/roast/). **A1)** Electric field magnitude modeling with a F7 cathode-right EC anode montage on a representative Bipolar Disorder participant from the study. **A2)** Electric field magnitude modeling with a CP1 cathode - right EC anode montage on a representative Bipolar Disorder participant from the study. **B1)** F7 e-field modeling using ROAST on the MNI Head. **B2**) CP1 e-field modeling using ROAST on the MNI Head. **C1)** The white circle on the human head shows the F7 electrode position in the 10-10 EEG system .**C2)** The white circle on the human head shows the CP1 electrode position in the 10-10 EEG system. All models used 5.8 cm diameter electrodes and −1mA current; color bar: v/m (Supplement for simulation details, subcortical slices, and additional head models)

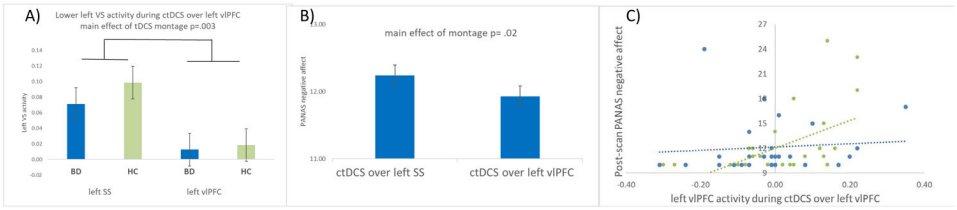

Figure 3.

A) Bar graphs with standard error of left ventral striatal activity (F(1,51)=9.61, p=.003) to reward expectancy during cathodal tDCS over the left vlPFC versus the left SS in Bipolar Disorder and healthy participants. B) Bar graph with standard error of pre-scan negative affect and post-scan negative affect (PANAS scores). Main effect of montage on post scan negative affect controlling for pre scan negative affect, following cathodal tDCS over the left vlPFC versus the left SS in all participants (F(1,49)=5.57, p=.02). C) The relationship between left vlPFC activity during cathodal tDCS over the left vlPFC and post-scan negative affect following cathodal tDCS over the left vlPFC. Bipolar Disorder participants in blue and healthy participants in green. Left vlPFC activity explained 8.2% of the variance in post-scan negative affect. Abbreviation: ctDCS= cathodal transcranial direct current stimulation, VS= ventral striatum, vlPFC = ventrolateral prefrontal cortex, SS = somatosensory cortex, Panas= Positive and negative affect schedule.

Table 1.

Demographic and clinical information. Anxiety scale = Hamilton Rating Scale for Anxiety, Depression scale = Hamilton Rating Scale for Depression, Mania Scale = Young Mania Rating Scale, BPRS = Brief Psychiatric Rating Scale. Mean (SD) or frequency (percentage) are reported.

	Healthy Control	**Bipolar Disorder I Remitted**		
	n=31	**n=27**	**statistic**	**p value**
age	27.7(5.7)	29.4(8.5)	t(44.6)=−.893	0.377
sex (F)	19 (61.3%)	17 (62.9%)	x2(1)=.000	1
IQ	111(6.6)	110.8(7.6)	t(55)=.132	0.895
Anxiety Scan 1	1.58(1.57)	3.48(2.83)	t(39.2)=−3.1	0.004
Anxiety Scan 2	1.16(1.7)	3.33(3.5)	t(37.1)=−2.96	0.005
Depression Scan 1	1.29(1.32)	2.93(1.49)	t(56)=−4.42	<.001
Depression Scan 2	1.39(1.7)	3.30(3.3)	t(37.3)=−2.7	0.01
Mania Scan 1	.16(.52)	.74(1.3)	t(33.7)=−2.23	0.032
Mania Scan 2	.07(.36)	.70(1.86)	t(27.7)=−1.76	0.089
BPRS Scan 1	18.19(.48)	19.56(1.34)	t(31.7)=−5.01	<.001
BPRS Scan 2	18.42(1.1)	19.33(2.5)	t(34.4)=−1.75	0.089
On medications				
Benzodiazepines	n/a	5 (18.5%)		
Mood Stabilizers	n/a	18 (66.7%)		
Antipsychotic	n/a	3 (11.1%)		
Antidepressant	n/a	5 (18.5%)		

Table 2.

Results of repeated measures ANOVA comparing tDCS (left vlPFC vs left SS) in Bipolar Disorder and healthy participants on primary and secondary neural measures. Abbreviations: ventrolateral prefrontal cortex (vlPFC), ventral striatum (VS), orbitofrontal cortex (OFC), d/rACC (dorsal/rostral anterior cingulate cortex (BA 24 and BA 32), somatosensory cortex (SS), transcranial direct current stimulation (tDCS).

	Effect of montage		Effect of group		montage × group interaction	
Primary neural measures	**F(1,51) =**	**p=**	**F(1,51) =**	**p=**	**F(1,51) =**	**p=**
Activity						
left VS	9.61	.003*	.20	.656	.34	.563
right VS	5.00	.030	.10	.759	.10	.751
left vlPFC	.31	.583	1.47	.213	.50	.481
Functional connectivity						
left vlPFC-left VS FC	4.99	.030	.06	.806	.50	.482
left vlPFC-right VS FC	3.56	.065	.39	.536	.81	.372
Secondary neural measures						
Activity						
left amygdala	5.29	.026	.89	.349	2.20	.145
right amygdala	4.66	.036	1.16	.286	8.86	.004*
left BA 24	7.15	.010*	.01	.920	1.67	.202
right BA 24	8.24	.006*	.01	.932	1.53	.222
left BA 32	8.58	.005*	.45	.507	2.39	.128
right BA 32	6.01	.018	.00	.966	.42	.522
left OFC	1.27	.265	.55	.464	.36	.554
Functional connectivity						
left vlPFC seed						
left vlPFC-left amygdala	.00	.949	.13	.722	.37	.546
left vlPFC-right amygdala	.02	.892	1.26	.268	2.04	.159
left vlPFC-left BA24	.38	.542	5.02	.029	.02	.877
left vlPFC-right BA24	1.62	.209	5.48	.023	.17	.678
left vlPFC-left BA32	.15	.703	.60	.443	1.37	.247
left vlPFC-right BA32	1.14	.290	5.09	.028	.19	.666
left vlPFC-left OFC	.44	.512	.14	.714	.19	.664

*FDR corrected p-value = .01