Effects of prefrontal tDCS on dopamine-mediated behavior and psychophysiology

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Abstract

The ability to manipulate dopamine *in vivo* through non-invasive, reversible mechanisms has the potential to impact clinical, translational, and basic research. A recent PET study demonstrated that a single session of prefrontal transcranial direct current stimulation (tDCS) increased striatal dopamine binding. We sought to extend this work by examining whether prefrontal tDCS could increase both dopamine levels and behavior. We conducted a between-subjects study (n=30) using active and sham tDCS and used spontaneous eye blink rate as an indirect proxy for dopamine functioning. The initial design and analyses were pre-registered (https://osf.io/gmnpc). While stimulation did not show an effect for any of the basic pre-registered analyses, we identified individual differences suggesting that baseline dopamine has an effect on tDCS stimulation. Baseline dopamine was positively related to change in dopamine within the active stimulation group but negatively related to change within the sham stimulation group. While this pre-registered design involved a small sample size, it provides critical information about how studies of tDCS need to account for baseline dopamine levels when interpreting tDCS stimulation response.

Introduction

The ability to modulate brain activity and improve behavioral performance is a prominent objective in cognitive neuroscience research. Providing accessible and non-invasive means to do so remains a challenging endeavor that has yet to be completely accomplished. One promising method for non-invasive neuromodulation is transcranial direct current stimulation (tDCS). tDCS is capable of enhancing or inhibiting brain activity in a targeted area by altering neuronal firing rates and neurotransmitter concentrations [1–3]. This method has also been shown to induce a reorganization of functional networks and impact neuroplasticity [4,5]. However, the efficacy of tDCS is related to individual differences in various factors such as genetic makeup and baseline neurochemical states [6–8]. Evidence suggests that there are disparities in responsiveness to tDCS, indicating that some individuals may be more receptive to non-invasive brain stimulation than others and that this method may, therefore, exert differing effects on cognitive performance [9–11]. Further, it has been demonstrated that the effect of tDCS on executive function, for instance, is dependent upon methodological characteristics such as cathode location and anode size, as well as other stimulation parameters[12,13]. Thus, inconsistent findings from the work employing tDCS could be a partial product of inter-individual variability and discrepancies in replicating stimulation montages.

Specifically, our interests in neuromodulation lie with the dopaminergic midbrain as this area is implicated in a variety of cognitive behaviors (e.g., reward-based decision making, learning, and motivated behavior), as well as disease pathology and aging [14,15]. Influencing the neurochemistry of this brain area using a method such as tDCS could contribute to therapeutic advances targeting dopamine-related behaviors, and diseases involving dopaminergic dysfunction. Notably, the midbrain is both directly and indirectly linked to the prefrontal cortex via dopaminergic pathways [16–19]. Thus, prefrontal stimulation may be effective in manipulating dopaminergic function and influencing activity in the midbrain through modulation of these

dopamine-driven connections. Indeed, prefrontal stimulation has been shown to improve symptoms in dopamine-related disorders such as Parkinson's disease and schizophrenia [20–22]. However, further research is necessary to better understand the impact of this non-invasive method in healthy adults and the significance of individual differences in determining its effects.

Recent work has suggested that prefrontal stimulation does indeed show a great deal of promise in healthy individuals. Combining tDCS to the left and right dorsolateral prefrontal cortex (DLPFC) with positron emission tomography (PET), Fonteneau and colleagues (2018) demonstrated that stimulation increases dopamine levels in the ventral striatum. In addition, tDCS and imaging research has shown that frontal stimulation increases signal intensities in associated striatal areas, specifically in the nucleus accumbens [1,24]. Relatedly, clinical studies using repetitive transcranial magnetic stimulation (rTMS) have also increased dopamine release in the striatum as a consequence of prefrontal stimulation [25,26]. The developing consensus from these studies is that modulation of the meso-cortico-limbic pathway may be a possible mechanism of action as it connects the midbrain to DLPFC pathways with the ventral striatum. Importantly, this suggests that stimulation to the DLPFC may impact downstream dopaminergic systems in the midbrain as well.

Therefore, we conducted a study employing anodal tDCS applied to the prefrontal cortex with the intent of affecting dopaminergic pathways that lead to the midbrain. To investigate the interplay between individual differences in responsiveness to tDCS and the effect of stimulation, we used a mixed design wherein stimulation condition (active anodal or sham) was implemented as a between subjects variable, while behavioral and physiological data was collected both before and after stimulation as a within subjects variable. Both pre- and post-tDCS, we employed physiological recording of spontaneous eye-blink rate and two behavioral tasks that have been previously associated with dopaminergic function. The behavioral measures included a reward paradigm using facial attractiveness ratings, as this particular task has demonstrated an association with midbrain activity [24]. Stimulation of the prefrontal cortex

with tDCS has been successful in increasing appraisals of facial attractiveness, presumably by way of remotely activating the dopaminergic pathways that lead to the midbrain [24]. Research has also shown that facial attractiveness paradigms activate reward circuitry through corticostriatal dopaminergic pathways, further supporting the adoption of this specific task as a dopamine correlate [27–29]. In addition, reward-related brain regions have been shown to express a linear change in activity with increasing or decreasing attractiveness judgments, though some of these regions are preferentially responsive based on the subjects' gender [27].

The second task was based off of the idea that orienting bias in visual attention is indicative of D2 receptor asymmetries in the striatum [30]. Orienting bias toward the left visual hemispace, specifically, is thought to arise from a right hemispheric specialization in the processing of spatial information. This relationship is substantiated by PET evidence exhibiting that pseudoneglect, or the natural tendency to shift visual attention to the left hemispace, reflects disparities in the lateralization of dopaminergic systems in the striatum [31]. Additionally, differences in spatial attention have been predicted by genetic variations of the dopamine transporter gene [6,32]. Thus, the degree to which an individual maintains a leftward orienting bias can be used as an additional variable to inform differences in dopaminergic activity.

Finally, we used spontaneous eye blink rate (EBR) as a physiological proxy for striatal dopamine levels. Baseline blink rate and tonic dopamine activity have been positively correlated in a number of studies [33–35]. Further, neuroimaging work has demonstrated a link between EBR and dopamine D2 receptors [36], though more recent PET studies have failed to replicate these findings [37,38]. However, both D1 and D2 agonists have been implicated in a dose-dependent relationship with EBR [39–42], and current research continues to employ this method as an indirect measure of tonic dopamine functioning [43]. As such, recording eye muscle activity enables us to calculate a standard blink rate and gauge individual differences in baseline dopamine levels. We implemented the described measures as a multilayered index of tonic dopamine to better understand the impact of bifrontal non-invasive brain stimulation on midbrain dopamine levels.

We predicted that active anodal tDCS would increase midbrain dopamine levels as evidenced by a parallel impact on behavior and physiology. More specifically, we expected higher ratings on the facial attractiveness paradigm and a decrease in leftward attentional bias following active stimulation relative to sham, as well as an increase in average EBR. These hypotheses are in consideration of reward circuitry activation via corticostriatal pathways and reduced striatal receptor asymmetries as a result of increased midbrain dopamine activity [27–31]. However, taking individual differences into account, we further predicted that baseline dopamine levels, as quantified by behavioral performance proxies, would impact responsiveness to tDCS and, in turn, the distribution of performance differences following stimulation administration. This hypothesis was formulated in light of evidence wherein inter-individual differences in baseline dopamine, as a product of genetic variability, were shown to influence behavioral outcomes such as attentional bias and activation of reward systems [6–8]. Our experimental design and outline for *a priori* analyses were pre-registered on Open Science Framework before data collection commenced.

Methods

Participants

Thirty-four healthy young adults participated in the study. Four participants were excluded from analyses due to technical difficulties with data collection (n = 1), discomfort from stimulation administration (n = 1), or issues establishing an adequate connection (n = 2) as thick, curly hair can obstruct electrodes when using the particular montage employed here. As such, our final sample included thirty participants (mean age = 22.43 $\pm$ 3.15 years, 11 female). All subjects were right-handed and did not have a history of neurological illness. In addition, none of the participants were taking medication that may affect the central nervous system and all were screened according to the IRB approved exclusion criteria associated with tDCS [5]. Participation was limited to those that had not completed other studies involving tDCS in the past. Recruitment was executed through either the Texas A&M University Psychology Subject

Pool or bulk email, and all subjects were compensated $10/hour for participation. Those recruited through the Texas A&M University Psychology Subject Pool received compensation, as previously noted, rather than course credit for their participation in order to keep study procedures consistent. All procedures were approved by the Institutional Review Board at Texas A&M University, and written informed consent was obtained from all participants.

Transcranial Direct Current Stimulation

We used a mixed design with stimulation condition as a between subjects variable. Each subject participated in only one session and received either sham or active anodal stimulation. Participants were randomly assigned to a stimulation group upon enrollment in the study. All participants were blinded to the condition until the debriefing period at the end of the study. tDCS was administered using a Soterix 1x1 Low Intensity transcranial electrical stimulator and two 5cm x 7cm sponges soaked in saline (Soterix Medical, New York, NY). An electrode was placed inside each sponge and attached to the scalp using elastic bands. The electrodes were placed on F3 and F4, the areas corresponding to the left dorsolateral prefrontal cortex (lDLPFC) and right dorsolateral prefrontal cortex (rDLPFC), respectively, according to the 10-20 measurement system. An anode was used for the lDLPFC while a cathode was used for the rDLPFC, producing a bifrontal stimulation montage, replicating Fonteneau et al. (2018). An initial stimulation of 1.0mA was delivered for 30 seconds in each session regardless of stimulation condition, allowing the current to break through the scalp and establish a consistent connection. Once an adequate connection was established, stimulation began and current gradually increased until the desired intensity of 2.0mA was reached. tDCS was administered at a steady 2.0mA for a period of 20 minutes during the active stimulation sessions. During sham stimulation, however, participants only experienced a current of 2.0mA at the first and last 30 seconds of the 20 minute period while a current of 0mA was delivered for the remaining time in these sessions. This procedure was implemented in order to prevent subjects' detection of the stimulation condition. In order to assess the effectiveness of this sham procedure, questions

concerning the subjects' perception of stimulation condition were included in a final survey at the end of the session before the condition received was fully disclosed.

Behavioral Assessments

Two behavioral tasks associated with dopaminergic activity were implemented both before and after tDCS administration in order to index any changes that may occur in response to stimulation. One task was modeled after a facial attractiveness rating paradigm by Chib and collegues (2013) where subjects were presented with a neutral-expression facial image and instructed to rate the attractiveness of that image on a scale of 1 to 7. A rating of "1" would indicate a low attractiveness score whereas a rating of "7" indicated a high score of attractiveness. These ratings were made using a computer keyboard as the participant completed 72 trials both before and after tDCS administration for a total of 144 trials. The facial images were displayed on the computer screen until the participant made a response, at which point the next stimulus would be presented after an inter-stimulus interval of 1000 ms. These images were grouped and randomized such that each set, both before and after stimulation, was equal in mean attractiveness. The image sets were also generated to include an equal percentage of male and female faces and an equal proportion of Asian, Black, Latinx, and Caucasian faces using the Chicago Face Database, Version 2.0.3 [44]. This paradigm is associated with the dopaminergic reward system and, thus, an increase in facial attractiveness ratings after active brain stimulation would be indicative of an increase in dopaminergic activity. Therefore, we measured the difference in average attractiveness ratings between pre-tDCS and post-tDCS performance. These scores were based off of a normalized mean to account for consistently low ratings across all participants as practiced by Chib and collegues (2013).

Additionally, the greyscales paradigm (Figure 1) was used to assess the degree of leftward bias exhibited by each individual in regard to visuospatial attention, and all task parameters were in replication of Tomer and colleagues (2013). Two rectangles containing a black to white gradient were presented on a computer screen for 5000 ms and each subject was

instructed to choose the rectangle that appeared darker overall. After 5000 ms passed, the rectangles were whited-out and the next gradient stimulus was not presented until a response was made. If the participant made a response before the gradients became completely white, the trial was ended and the next stimulus appeared after an inter-stimulus interval of 1500 ms. The subject was advised to press a specific key on the computer keyboard associated with either the bottom rectangle, “B”, or top rectangle, “T”, when making their response. Following an initial practice portion of 12 trials, the task included 144 experimental trials [31] and was administered both before and after brain stimulation. In the first half of the trials, a difference in luminosity was present, but in the second half there was no actual difference between the rectangles. Leftward attentional bias was measured as the proportion of trials where the subject chose the rectangle with a gradient beginning on the left side as the darker stimulus overall when both rectangles were in fact the same. In addition, looking only at error trials where subjects failed to accurately respond, attentional bias was calculated for trials in which a difference in darkness was indeed present between rectangles. However, the latter calculation was specifically implemented as a supplementary assessment of orienting bias. An increase in dopaminergic activity following active tDCS would result in a reduction of leftward attentional bias after stimulation, relative to before as compared to sham stimulation where no difference would be expected. Therefore, dopaminergic modulation was indexed by the difference in leftward attentional bias between pre-tDCS and post-tDCS performance, and was compared between active and sham stimulation conditions.

Physiological Assessment

In addition to the behavioral assessments, spontaneous eye-blink rate (EBR) was recorded to investigate a physiological marker of dopaminergic activity. Using Ag/AgCl electrodes and a BIOPAC EOG100C Electrooculogram Amplifier, eye movements were recorded upon securing two receiving electrodes around the right eye and one ground electrode between the eyebrows (BIOPAC Systems, Inc., Goleta, CA). This setup allows for the rate of

eye blinks to be collected and analyzed for each subject to consider differences between baseline physiological functioning and post-stimulation functioning relative to sham. Participants were instructed to focus on, but not stare at, a fixation cross without engaging in any activity while their natural blink rate was recorded for a 5 minute period. This was preceded by a 30 second baseline recording where markings distinguishing between eye movements and eye blinks were made to assist in subsequent data analysis. This procedure was repeated again after tDCS was administered, and blinks were manually counted by multiple raters before a blink rate average per 30 second interval was calculated for each subject. Inter-rater reliability for the total number of blinks during each 5 minute recording was very high (r = 0.99).

Procedure

Upon arrival, participants were given a brief overview of the study procedures and completed a consent form. Participants then performed the greyscales and facial attractiveness tasks to provide baseline behavioral assessments. The order of these tasks was counterbalanced across all subjects. Once both tasks were completed, EBR setup began and recordings were conducted for a period of 5 minutes while the participant fixated on a cross as instructed. Following this period, the EBR electrodes were disconnected from the amplifier but left attached to the subject during tDCS administration to keep placements consistent and minimize variability between pre and post recordings. Participants then received 20 minutes of either sham or active stimulation, based on random stimulation group assignment. After tDCS was completed, the equipment was removed and a brief demographic survey was administered. EBR electrodes were then reconnected to the amplifier to complete another 5 minute period of eye blink recordings before a second round of the same behavioral tasks took place. In addition, a questionnaire regarding sensations from the brain stimulation portion was administered to collect information on the subjects' experience. Finally, each participant was debriefed on the purpose of the study and the stimulation condition was revealed.

Data Analyses

All analyses not listed as exploratory were pre-registered, along with the study design, on Open Science Framework (https://osf.io/gmnpc). Independent samples t-tests were used to assess the effects of stimulation condition on each dopamine correlate individually, where the dependent variable was change in the measure (post stimulation - pre stimulation). Independent samples t-tests were also used to compare measures across stimulation groups prior to stimulation to ensure that any difference in the post-stimulation measures was not due to group differences prior to stimulation.

Because mean facial attractiveness ratings were skewed towards the lower end of the rating scale (*M* = 3.18, *Max* = 4.72, *Min* = 1.08), attractiveness ratings were max-normalized following Chib and colleagues (2013). All subsequent references to attractiveness ratings refer to these max-normalized ratings. Additional analyses regarding the gender of the faces and participants' sexual preference can be found in the supplemental materials.

Previous work relating leftward bias on the greyscales task to dopamine systems has focused primarily on bias in trials on which there is no difference in darkness between stimuli [6,30,31,45]. However, previous work has also shown that on greyscales trials in which there is a difference between the darkness of stimuli, the leftward bias on error trials is correlated with leftward bias on trials with equally dark stimuli and might also be related to striatal dopamine [46,47]. Therefore, we examine in the main manuscript the effect of stimulation on bias in trials where there is no difference between stimuli, but bias on trials on which there is a difference is examined in the supplementary materials. Leftward bias was calculated as the percent of trials on which the rectangle that was darker on the left was chosen. On trials in which there was no difference in darkness between the two stimuli, participants displayed a leftward bias prior to the stimulation period (*M* = 64.58%, *SD* = 20.38%), after the stimulation period (*M* = 63.89%, *SD* = 25.41%), and across both time points (*M* = 64.24%, *SD* = 22.84%).

Sham stimulation effectiveness was first assessed by examining the survey question that asked which condition participants believed they were in. A chi square test of independence was used to examine whether a participants' stimulation condition affected their answer. Next, participants' ratings of each sensation during stimulation were analyzed as a function of stimulation condition using independent t-tests.

To examine whether the effect of tDCS might depend upon baseline dopamine, we conducted exploratory regression analyses in which the IVs were stimulation condition and a baseline behavioral measure and the DV was change in another behavioral measure (post-stimulation minus pre-stimulation). All p-values reported in the following tests are false-discovery rate (FDR) corrected (p_{ADJ}).

As initial exploratory analyses examining the interaction between a participants' baseline task performance (indicators of baseline dopamine) and the effect of stimulation, six regression models were fitted. For each model, change in one behavioral measure was the dependent variable. The independent variables were baseline (pre-stimulation) performance on a separate task and stimulation condition. To quantify baseline dopamine levels, each participant's pre-stimulation measures were converted to z-scores. Because lower leftward bias scores indicated higher dopamine levels, the signs for leftward bias z-scores were inverted so that more positive z-scores always indicated higher baseline dopamine. A composite baseline dopamine score was then created by averaging the z-scores from all three measures for each participant. Three regression models were then examined; for each, the IVs were stimulation condition and composite baseline dopamine score, while the DV was the change in one of the behavioral measures.

Results

Greyscales task

There was no significant difference across stimulation groups in leftward bias prior to stimulation, $t(27.90) = 0.50$, $p = .62$. There was also no effect of stimulation condition on change in leftward bias, $t(19.72) = 1.27$, $p = .22$, $d = 0.47$. However, the active stimulation group exhibited a greater decrease in bias following stimulation (M = -8.02%, SD = 19.89%) than the sham stimulation group (M = -2.52%, SD = 17.41%), in line with predictions.

Facial attractiveness ratings

There was no significant difference across stimulation groups in attractiveness ratings prior to stimulation, $t(24.45) = 0.05$, $p = .96$. There was no effect of stimulation condition on change in attractiveness ratings, $t(23.73) = 0.64$, $p = .53$, $d = 0.23$. The active stimulation group showed a more positive change in ratings (M = 0.01, SD = 0.09) following the stimulation period compared to the sham stimulation group (M = -0.01, SD = 0.05), in line with hypotheses.

EBR

Across stimulation groups, there was no significant difference in EBR prior to stimulation, $t(29.97) = 0.31$, $p = .76$. There was no effect of stimulation on change in EBR ($t(24.31) = 1.19$, $p = .25$, $d = 0.42$). However, there was a larger increase in EBR following active stimulation (M = 3.99, SD = 9.81) compared to sham stimulation (M = 0.59, SD = 5.79), consistent with predictions.

Baseline Dopamine and Stimulation Effects

There was no significant interaction between baseline EBR and stimulation condition ($p_{ADJ} = .87$) nor between baseline attractiveness ratings and stimulation condition ($p_{ADJ} = .21$) in predicting change in greyscales bias. Additionally, there was no significant interaction between baseline EBR and stimulation condition ($p_{ADJ} = .69$) nor between baseline greyscales bias and stimulation condition ($p_{ADJ} = .21$) in predicting change in facial attractiveness ratings.

However, stimulation condition and baseline attractiveness ratings significantly interacted to predict change in EBR (β = -0.94, p_{ADJ} = .03). Within the active stimulation condition, participants who made higher attractiveness ratings prior to stimulation displayed a greater increase in EBR following stimulation (r = .70, p_{ADJ} = .02), whereas this relationship was weaker and in the opposite direction in the sham stimulation group (r = -.25, p_{ADJ} = .38). The direction of these relationships indicated that baseline dopamine was positively related to change in EBR within the active stimulation group. Additionally, stimulation condition and baseline greyscales bias interacted to predict change in EBR, although following multiple comparisons corrections the significance reached only a trend level (β = 0.84, p_{ADJ} = .06). However, the direction of these relationships also indicated that greater baseline dopamine predicted a greater change in EBR in the active stimulation group while the opposite was true in the sham stimulation group; greater changes in EBR were associated with a nonsignificant decreased leftward bias in the active stimulation group (r = -.31, p_{ADJ} = .87), while this relationship was reversed in the sham stimulation group (r = .67, p_{ADJ} = .21).

When all three correlates were aggregated to assess overall baseline dopamine, there was a significant interaction between stimulation condition and composite baseline dopamine in predicting change in EBR (β = -1.19, p_{ADJ} = .009; see Figure 2). Within participants that received active stimulation, change in EBR was positively correlated with composite baseline dopamine score (r = .72, p_{ADJ} = .01). Within participants that received sham stimulation, change in EBR was not significantly related to composite baseline dopamine score (r = -.52, p_{ADJ} = .10). There was no significant interaction between stimulation condition and composite baseline dopamine score on either of the other behavioral measures (ps_{ADJ} > .10).

Data Sharing

All data and scripts used for this study are available on Open Science Framework (https://osf.io/zhjys/).

Discussion

Individual differences in response to tDCS have been well documented [9–11,48–50]. However, the biological mechanisms behind these individual differences are not fully understood. Building upon work by Fontenau and colleagues (2018) that documented an increase in striatal dopamine at D2 receptors following bilateral DLPFC stimulation, the current work examined the effects of bilateral DLPFC stimulation on three correlates of dopamine function (facial attractiveness ratings, visuospatial bias, and EBR) as a function of baseline dopamine (operationalized by aggregating the three behavioral correlates). Unexpectedly, stimulation did not uniformly affect the dopamine correlates across the sample. However, within the active stimulation group, there was a significant positive relationship between baseline dopamine and the change in EBR following stimulation. This relationship was not significant within the sham stimulation group. The results suggest that stimulation is more effective in increasing EBR for participants with higher baseline dopamine levels than participants with lower baseline dopamine levels.

The positive correlation between baseline dopamine measures and change in EBR is in line with previous work examining the effects of dopamine agonists on EBR, although such work is scarce. Groman (2014) found a positive relationship between EBR and striatal dopamine receptor density as well as a positive relationship between receptor density and change in EBR following the administration of a dopamine agonist. This may provide a mechanistic account for our results here, though it is speculative. Participants with high baseline dopamine measures might possess a greater density of striatal dopamine receptors for the stimulation to act upon, resulting in a larger effect of stimulation.

Genetic differences related to receptor density might also underlie individual differences in responsiveness to tDCS. Participants with reduced leftward visuospatial bias (conceptualized in this study as an indication of high baseline dopamine) are more likely to possess the TaqI A1 allele of the DRD2 gene [6], which is related to higher self-report measures of reward

responsiveness [51] and alcoholism [52]. Crucially, individuals possessing the TaqI A1 allele have previously displayed greater responses to dopamine agonists [7], which might explain, at least in part, the baseline dopamine effects in the current work. Individuals characterized as 'high baseline dopamine' by our behavioral measures (particularly leftward bias and facial attractiveness ratings) might be more likely to carry the TaqI A1 allele. However, the relationship between DRD2 and the effects of tDCS has not yet been explored. Genes related to enzymatic breakdown of dopamine, such as COMT, might also contribute to the individual differences in dopaminergic response to tDCS. However, while COMT has been found to modulate the effects of tDCS on behavior [8–10,48], further work is needed to assess its relationship with the dopamine correlates used in the current work.

In contrast to the current study, previous PET work found no interaction between baseline dopamine and dopaminergic response to bilateral DLPFC stimulation [23]. However, the study only examined dopamine binding at D2-like (D2, D3 and D4) receptors. Our composite baseline dopamine score might additionally measure tonic dopamine at D1-like receptors (D1 and D5), which could account for the discrepancy between the results of the studies. A number of studies have linked EBR to both D1-like and D2-like receptor activity [39–41]. However, no previous work has examined the relationships between visuospatial bias or facial attractiveness ratings and D1-like receptors. While it is possible that our baseline dopamine composite captures both D1-like and D2-like activity, accounting for differences between the conclusions of the current work and those of Fontenau and colleagues, this cannot be established with certainty.

The current work failed to replicate a previous study that found an increase in facial attractiveness ratings following prefrontal stimulation [24]. This might be due to differences in stimulation montage; while the current work employed a bilateral DLPFC montage, Chib and colleagues placed their anode over the ventromedial prefrontal cortex. Imaging-based parcellations of the striatum, however, indicate that the medial PFC and the DLPFC project to

different areas of the striatum [53,54]. Further, fMRI studies have consistently linked facial attractiveness ratings to activations in the striatum and medial areas of the prefrontal cortex [28,29,55]. Although facial attractiveness ratings still contribute to a measure of overall dopaminergic striatal activity, the bilateral DLPFC montage likely stimulated striatal circuits that are unrelated to facial attractiveness ratings.

Alternatively, the preferential effects of stimulation on EBR might be due to the order in which the measures were taken. EBR was always the first measurement after the stimulation period, followed by the other two tasks in a counterbalanced order. We chose this design to keep the timing of the experiment consistent. Prior work indicates that tDCS increases dopamine for up to 35 minutes after stimulation [23], but longer periods of time have not been examined directly. To ensure participants completed all tasks within the 35 minutes following stimulation, EBR was measured first so that the facial electrodes did not need to be reapplied following stimulation, which can take varying amounts of time. However, if the effects of stimulation are more short-lived than prior work suggests, they might be most apparent for EBR simply because it was always measured first.

The main limitation of the current work is the lack of direct measures of dopaminergic activity. While the measures used in the current paper have been consistently linked to dopamine systems and reward-related behavior [28,29,55,56,30,31,34,35,39–42], they are nonetheless indirect measures of dopamine function. Future work should build upon the work of Fonteneau by examining the effects of bilateral tDCS stimulation on D1-like receptors in the striatum as well as in-depth analyses of its effects on striatocortical network function rather than solely striatal function.

The sample size in the current work as also relatively small, particularly for individual differences research. However, the sample size was determined and pre-registered only with full-sample analyses in mind. Further, it should be noted that the effect sizes of the relationship between baseline dopamine and the effect of stimulation on EBR were rather large. In any case,

future work should attempt to replicate this result in other samples as well as examine the effects of stimulation on each individual measure in larger, higher powered samples.

Furthermore, the baseline dopamine aggregate measure used in the current work is a coarse measure. It is possible that 'high dopamine' individuals identified by the aggregate used here are heterogeneous with respect to striatal and PFC dopamine; some individuals identified as 'high dopamine' might be high in PFC dopamine, while others might be high in striatal dopamine. A more fine-grained analysis of the relationship between baseline dopamine in each area and the effect of stimulation would be beneficial.

While a growing body of evidence has established the contributions of dopamine-related genes to stimulation's effects on behavior, the results of the current work suggest that the degree to which stimulation affects dopamine itself might depend on similar baseline measures. More work examining the interaction between baseline dopamine, dopamine changes, and behavioral changes following tDCS (particularly with respect to D1-like receptors) is necessary to fully understand dopamine-related individual differences in tDCS responsiveness. Similarly, future studies should examine the effect of other tDCS montages, such as unilateral DLPFC stimulation, on the dopamine system as a function of baseline dopamine.

Understanding how baseline dopamine levels affect an individual's response to stimulation can aid researchers that hope to modulate behavior as well as clinicians that hope to treat disorders using tDCS. Previous work examining the effectiveness in treating depression using tDCS, for example, has yielded conflicting results [57]; baseline dopamine differences across samples might account for some of these differences. Moreover, a previous meta-analysis concluded that tDCS was effective in modulating executive function in clinical, but not healthy, populations [13]; baseline neurotransmitter differences between the two groups may account for this difference as well. In any case, controlling for dopamine levels at baseline might help identify individuals for which tDCS is maximally effective, or not effective, in modulating behavior and treating disorders.

The current work provides the first evidence that the effects of tDCS on the dopamine system depend upon an individual's dopamine level at baseline. An individual's baseline dopamine activity was positively correlated with the degree to which tDCS modified EBR, a marker of central dopamine. These results add to a quickly growing body of work that demonstrates significant differences in the effectiveness of tDCS across individuals. Future work should examine the interaction between the effects of tDCS and dopamine within disordered individuals as well as with respect to specific dopamine receptor subtypes.

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Competing Interests

The authors declare no competing interests.

Author Contributions

Michael J. Imburgio collected and analyzed data, wrote the second half of the manuscript and contributed to study design. Hannah K. Ballard collected data and wrote the first half of the manuscript. Astin C. Cornwall oversaw EBR data collection and coded behavioral tasks. Darrell A. Worthy contributed to manuscript preparation. Jessica A. Bernard and Joseph M. Orr contributed to manuscript preparation and study design and conceived the study.

Data Availability

All data, analysis scripts and task code are publicly available on OpenScience Framework (https://osf.io/zhjys/).

Informed Consent

All research was performed in accordance with IRB regulations and informed consent was obtained from all participants.

Tables and Figures

Table 1. Demographics and Placebo Effectiveness

	Active (*n* = 15)	Sham (*n* = 15)
	Demographic Information	
Gender (F/M)	7/8	4/11
Age	23.27 (3.41)	21.60 (2.72)
	Sensation Questionnaire	
Itching	2.47 (1.12)	2.25 (1.12)
Pain	1.93 (0.88)	1.69 (0.79)
Burning	2.33 (1.23)	1.94 (1.00)
Warmth/Heat	2.20 (1.01)	2.13 (1.09)
Pinching	1.93 (1.16)	1.63 (0.89)
Metallic/Iron Taste	1.00 (0.00)	1.06 (0.25)
Fatigue	1.47 (0.52)	1.56 (0.96)
	Stimulation Awareness	
Real	9	9
Sham	1	2
I don't know	5	4

Notes: *Means and standard deviations are presented for age and each sensation. Sensations were rated on a scale from 1 to 7. Number of respondents that gave each answer for stimulation awareness question is presented.*

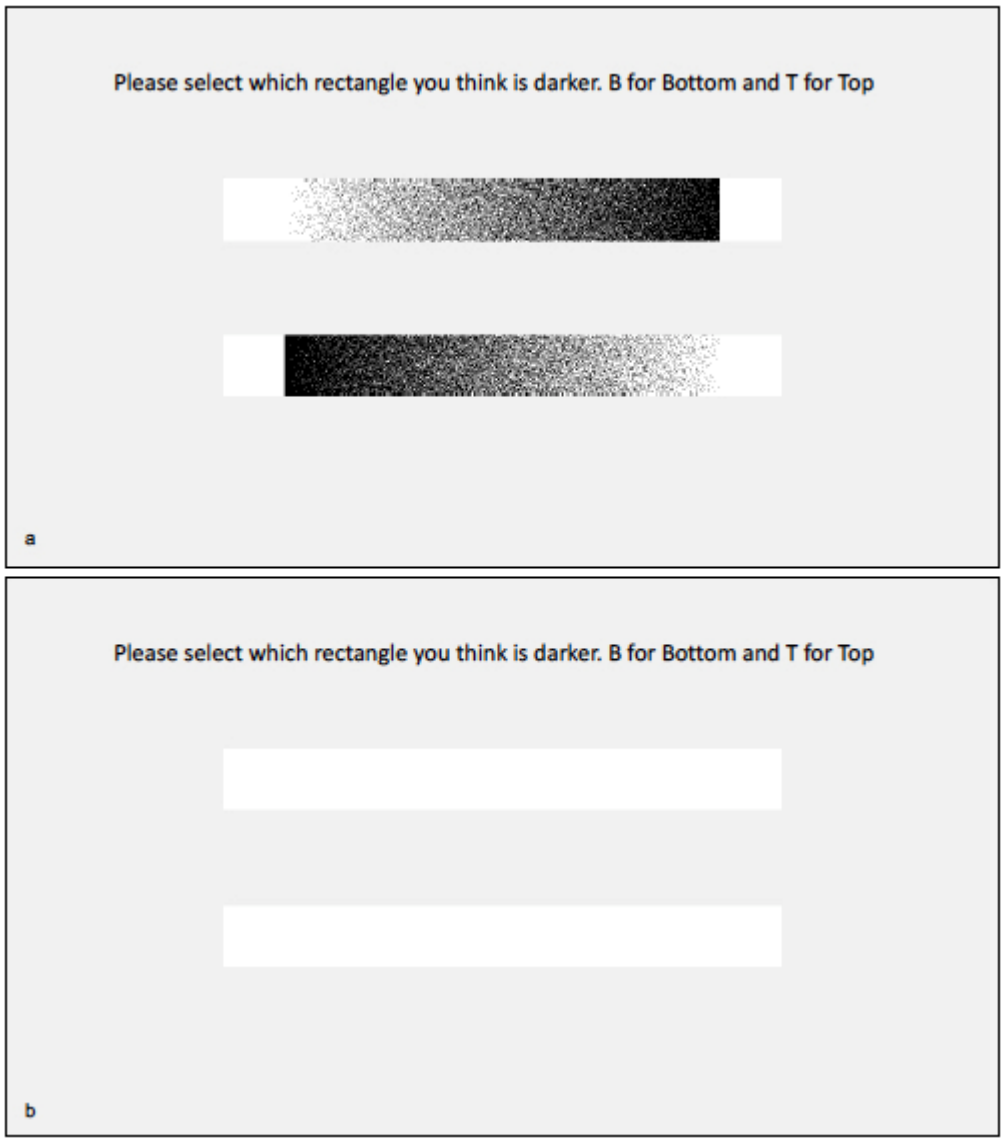

Figure 1. Greyscales paradigm. Participants were instructed to choose the rectangle that appeared darker overall using the "B" key for bottom and the "T" key for top on the computer keyboard (a). After 5000 ms passed, the rectangles were whited-out until the participant made a response (b). The task consisted of 144 trials, administered both before and after tDCS.

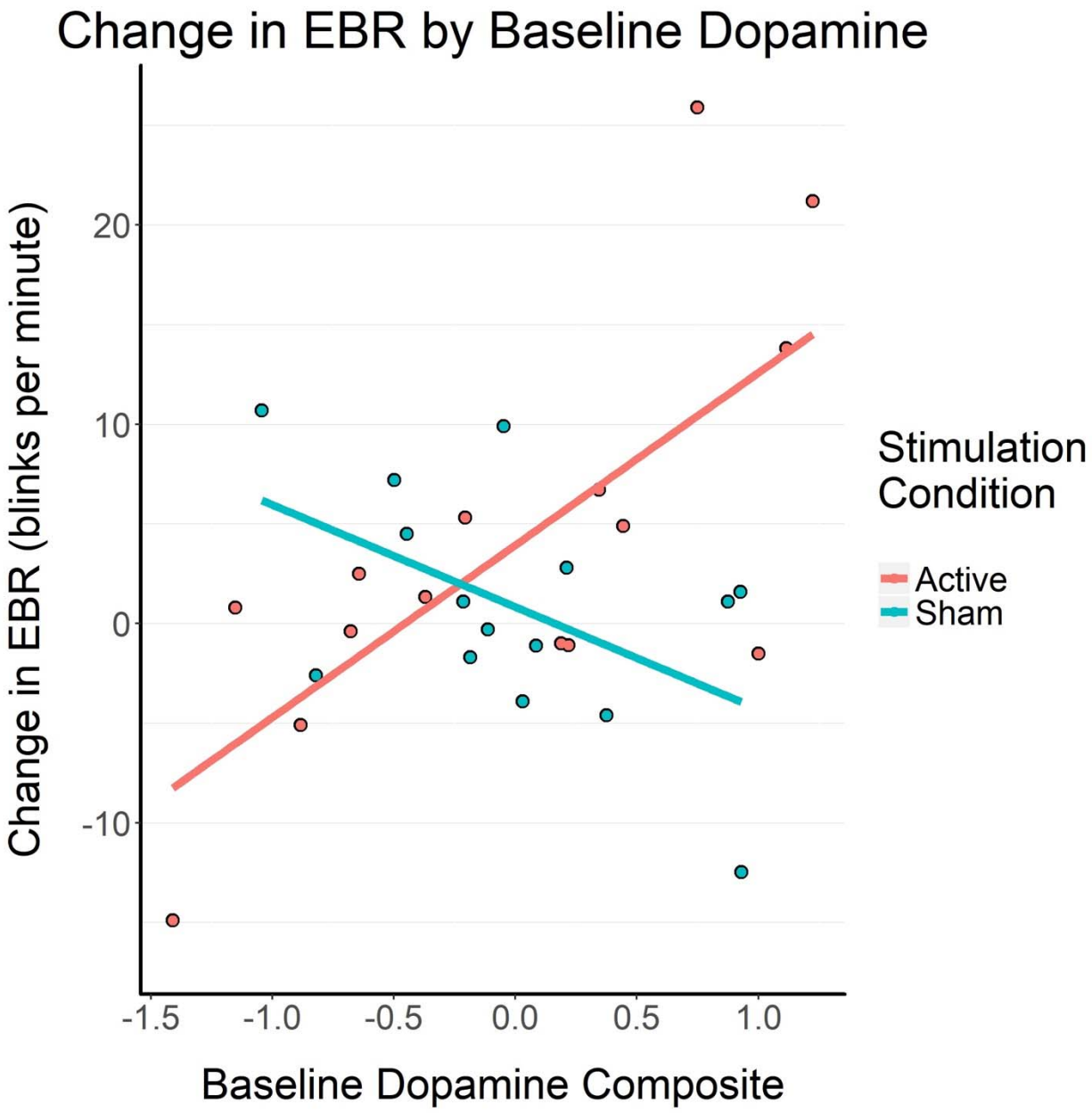

Figure 2. Interaction between baseline dopamine composite score and change in EBR following stimulation. Change in EBR following the stimulation period was positively correlated with baseline dopamine for the active stimulation participants, but not for the sham stimulation group.