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Effects of Transcranial Direct Current Stimulation on Visual Neuroplasticity in Schizophrenia

Carol Jahshan[1,2], Jonathan K. Wynn[1,2], Brian J. Roach[3,4], Daniel H. Mathalon[3,4], and Michael F. Green[1,2]

Abstract

People with schizophrenia (SZ) exhibit visual processing abnormalities that affect their daily functioning and remediating these deficits might help to improve functioning. Transcranial direct current stimulation (tDCS) is a potential tool for perceptual enhancement for this purpose, though there are no reports of tDCS applied to visual cortex in SZ. In a within-subject, crossover design, we evaluated the effects of tDCS on visual processing in 27 SZ. All patients received anodal, cathodal, or sham stimulation over the central occipital region in 3 visits separated by 1 week. In each visit, a backward masking task and an electroencephalography measure of visual neuroplasticity were administered after tDCS. Neuroplasticity was assessed with visual evoked potentials before and after tetanizing visual high-frequency stimulation. Masking performance was significantly poorer in the anodal and cathodal conditions compared with sham. Both anodal and cathodal stimulation increased the amplitude of P1 but did not change the plasticity index. We found significant plasticity effects of tDCS for only one waveform for one stimulation condition (P2 for anodal tDCS) which did not survive correction for multiple comparisons. The reason for the lack of tDCS stimulation effects on plasticity may be because tDCS was not delivered simultaneously with the tetanizing visual stimulus. The present findings emphasize the need for more research on the relevant parameters for stimulation of visual processing regions in clinical populations.

Keywords

schizophrenia, tDCS, visual plasticity, EEG, LTP

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Introduction

Patients with schizophrenia exhibit a wide range of visual system abnormalities, ranging from deficits in basic perceptual processes, such as backward masking and motion perception, to deficits in higher-level functions such as visual working memory.[1,2] These deficits contribute to social cognitive impairments and poor functioning seen in patients.[3,4] Thus, it is critical to evaluate the efficacy of innovative treatments that could enhance early perceptual processes in schizophrenia and, consequently, maximize improvements in functional outcomes.

Transcranial direct current stimulation (tDCS) is a noninvasive neuromodulation technique that uses weak electrical currents to alter the resting state of neuronal membrane potential.[5,6] tDCS changes the excitability of neurons in a polarity-dependent manner,[7] such that anodal stimulation enhances cortical excitability and cathodal stimulation decreases it.[8] Its low cost and ease of use makes tDCS an attractive treatment approach that might be relevant for improving visual processing in schizophrenia.

tDCS studies aimed at enhancing cognition in schizophrenia have commonly used a montage in which current is applied to the scalp over the dorsolateral prefrontal cortex, with encouraging findings for effects on working memory,[9] probabilistic association learning,[10] and composite scores on measures of cognition.[11] To date, one study suggests that tDCS could improve early sensory deficits (tone discrimination) in the auditory domain[12] in schizophrenia, but there are no reports of tDCS applied to the visual cortex to affect visual processing.

[1] Mental Illness Research, Education and Clinical Center (MIRECC), VA Greater Los Angeles Healthcare System, Los Angeles, CA, USA
[2] Semel Institute for Neuroscience and Human Behavior, University of California, Los Angeles, CA, USA
[3] San Francisco Department of Veterans Affairs Medical Center, San Francisco, CA, USA
[4] Department of Psychiatry, University of California, San Francisco, CA, USA

Corresponding Author:
Jonathan K. Wynn, Mental Illness Research, Education, and Clinical Center (MIRECC), VA Greater Los Angeles Healthcare System, Building 210, Room 221C, 11301 Wilshire Boulevard, Los Angeles, CA 90073, USA.
Email: jonathan.wynn@va.gov

Studies in healthy controls have demonstrated that visual functions can be transiently altered with tDCS applied to the visual cortex.[13,14] For example, anodal tDCS applied to regions such as V1 improved visual acuity,[15,16] contrast sensitivity,[17,18] orientation sensitivity,[19] and phosphene thresholds.[20,21] In addition to affecting behavioral performance on visual tasks, tDCS applied to the primary visual cortex can modulate early visual evoked potentials (VEPs), including the N70[22] and P100.[23] In response to low-contrast visual stimuli, the P100 amplitude increased after cathodal stimulation but decreased or stayed constant after anodal tDCS, whereas the opposite pattern was seen for the N70.

One potential mechanism for how tDCS affects cortical responding is via its effects on neuroplasticity.[24] There is evidence that tDCS affects the cellular and molecular mechanisms involved in long-term potentiation (LTP), a neural process thought to underlie learning and memory,[25,26] and its aftereffects seem to be *N*-methyl-D-aspartate (NMDA)–receptor dependent.[27] Additionally, tDCS has been shown to reduce surround suppression or GABAergic-mediated inhibition (a key modulator of plasticity) within the visual cortex.[28] Hence, tDCS appears to be a promising tool to influence neuroplasticity in humans.

Although numerous studies have demonstrated early perceptual changes with tDCS, none have taken advantage of new developments in neuroplasticity paradigms to directly examine the effects of tDCS on visual LTP in schizophrenia. While there are no standardized paradigms, all assess VEPs before and after some form of tetanizing visual stimulus (eg, rapidly presented at $\sim$9 Hz for 4 minutes, or repeated presentation at a slower 2 Hz for an extended period of time such as 10 minutes). These paradigms have recently been extended to clinical populations, such as in people with schizophrenia[29] or bipolar II disorder,[30] with evidence that LTP assessed in this manner is dysfunctional in these populations (though see Wynn et al,[31] where no dysfunctional LTP was found in people with schizophrenia).

In this study, we examined whether visual processing at the neural level can be engaged and modulated with tDCS of the occipital lobe in a sample of people with schizophrenia. To our knowledge, no previous study has applied tDCS to the visual cortex in this population and examined its effects. Specifically, we evaluated the effects of active tDCS, compared with control sham stimulation, on a behavioral measure of visual object masking and an EEG paradigm that measures LTP-like plasticity through repetitive visual stimulation.[32]

Methods

Study Design and Procedures

This was a 3-week within-subject, crossover, double-blind study conducted at the Veterans Affairs (VA) Greater Los Angeles Healthcare System (GLA) from July 2016 to May 2018. The study protocol was approved by the VA Institutional Review Board; all participants had the capacity to voluntarily consent to the procedures. Participants were randomly assigned to 1 of 6 sequences of stimulation condition counterbalanced for order. All patients received anodal, cathodal, and sham stimulation in 3 different visits separated by 1 week to washout any potential carryover effects. In each visit, they received a single stimulation followed by the EEG and behavioral tasks. The type of stimulation that each subject received on a particular visit was concealed from the subject as well as from the staff members who conducted the EEG and behavioral assessments. A urine toxicology screen was conducted at each assessment visit. In the rare instance when a subject tested positive, he or she was rescheduled to complete the assessments on another day. Participants were compensated $15 per hour and reimbursed for transportation.

Participants

Twenty-seven patients with schizophrenia were recruited from VA outpatient treatment clinics and board-and-care residences in the community. Participants were considered clinically stable based on the following: no medication changes in the past 6 weeks, no psychiatric hospitalization in the past 3 months, and no changes in housing in the past 2 months. Exclusion criteria included having an estimated premorbid IQ less than 70 based on reading ability, having an identifiable neurological disorder, seizures, or history of serious head injury with loss of consciousness longer than 15 minutes, meeting criteria for a substance use disorder of moderate or greater severity in the past 6 months, or being insufficiently fluent in English as determined by the participant's ability to understand the consent form.

All patients received a diagnostic interview with the Structured Clinical Interview for *DSM-5* (SCID-I[33]). Interviewers were trained to reliability through the Treatment Unit of the Department of Veterans Affairs VISN 22 Mental Illness Research, Education, and Clinical Center (MIRECC).[34] Clinical symptoms were evaluated using the expanded 24-item UCLA version of the Brief Psychiatric Rating Scale (BPRS[35]) and the Scale for the Assessment of Negative Symptoms (SANS[36]). The Role Functioning Scale (RFS[37]) was used to assess patients' functioning in the past month. Patients were also interviewed regarding the most common side effects typically reported following tDCS[38,39] after each stimulation session using a structured interview with symptom severity ratings (0 = none, 1 = mild, 2 = moderate, 3 = considerable, 4 = severe).

tDCS Procedure

tDCS was delivered by an Activa Dose II Iontophoresis Unit using a unilateral setup with one active 5 × 7 cm saline soaked sponge electrode and a single 5 × 7 cm reference electrode.

The active electrode was placed over the central occipital lobe (equivalent to electrode site Oz based on the 10/20 international system) and the reference electrode was placed over the lateral side of the right bicep. Two milliamperes of direct current was delivered for 20 minutes with a 30-second ramp-up and ramp-down period. In the sham condition, the current was turned on for 30 seconds and then ramped down to 0 mA. This sham procedure has been shown to be effective in simulating the sensation of active stimulation[40] minimizing the likelihood of unblinding. Participants sat in a comfortable chair and watched a movie while they received the tDCS. Immediately after tDCS ceased, the participant was setup for the EEG, which took no longer than 20 minutes, and then began the visual LTP task.

Outcome Measures

Visual LTP Paradigm.. All participants were assessed after their tDCS session using an EEG-based visual plasticity paradigm. This paradigm involved measurement of VEPs evoked by visual stimuli before and after tetanizing visual high-frequency stimulation (HFS) to assess input-specific LTP-like visual neuroplasticity. All stimuli were presented on a 23-inch LCD monitor (1920 × 1080 pixels, 60 Hz refresh rate) located 1 m in front of participants. Stimulus presentation and synchronization with the EEG was performed with Presentation version 17.2 (Neuro Behavioral Systems).

VEPs were assessed in four 6-minute runs: 12 and 6 minutes before HFS (pre-HFS) and 30 and 36 minutes after HFS (post-HFS). We did not assess VEPs in the period immediately following HFS (e.g., 2-6 minutes post HFS) as it has been found that repeated post-HFS stimulation can *depotentiate* the effect of tetanization, effectively cancelling out any potential LTP effects.[41] Each run included 266 trials in which participants were shown vertical and horizontal line gratings (133 of each). The line gratings were presented at fixation and subtended 15.9° × 17.1° of visual angle (horizontal × vertical). The dark and light stripes were reversed on every other presentation to minimize adaptation effects. Stimuli were presented at an intertrial interval (ITI) of 1067 to 1333 ms (1200 ms average) for variable durations (ranging from 250 to 500 ms, with an average duration of 375 ms) to minimize the influence of offset potentials on the VEPs. On 90.2% of the trials, the line gratings were presented with 35% contrast; on the remaining trials, contrast was set to 72%. To ensure that participants were paying attention during the task, they were instructed to push a button on a game controller whenever they saw the infrequent higher contrast gratings. Examples of the stimuli and the sequence of VEP assessments can be seen in Wynn et al.[31]

After the 2 pre-HFS VEP runs, HFS was administered. In HFS, stimuli were rapidly presented at 10 Hz for 5 seconds, followed by a 5-second blank screen, and this sequence was repeated for 4 minutes. To assess input specificity of any HFS-induced plasticity effects, participants were randomly assigned to receive HFS with only 1 of the 2 line grating orientations (ie, vertical or horizontal). As with the VEP runs, participants were instructed to push a button on a game controller when they saw the infrequent higher contrast stimulus.

For analysis, VEPs were averaged separately for pre- and post-HFS VEP runs (collapsing across the 2 runs for each) and for tetanized (ie, line orientation used in HFS) and nontetanized (ie, line orientation not used in HFS) stimuli. We also examined nonspecific plasticity effects (ie, regardless of tetanized stimuli) by averaging over tetanized and nontetanized stimuli.

EEG Acquisition and Processing.. Continuous EEG was recorded using a custom electrode cap (Cortech Solutions) and an ActiveTwo BioSemi amplifier (BioSemi). Each active electrode was measured online with respect to a common mode sense electrode during data collection, forming a monopolar channel. Data were sampled at 1024 Hz and re-referenced offline to Fz. Data processing was performed using BrainVision Analyzer 2 (Brain Products). A high-pass filter at 1 Hz (zero phase shift, 24 dB/octave rolloff) was applied to the raw EEG data. VEOG and HEOG eye movement and blink activity were removed from the EEG data using a regression-based algorithm.[42] Data were low-pass filtered at 20 Hz (24 dB/octave), epoched from −100 to 500 ms, then baseline corrected using the −100 to 0 ms time period. Epochs that contained activity exceeding ±75 μV at any electrode site were automatically rejected. After data processing and cleaning, separate waveforms were created for the pre-HFS and post-HFS period by tetanized and nontetanized stimuli. Based on visual inspection of grand averages from all subjects/conditions, we extracted the mean activity for 3 VEPs: between 98 and 118 ms for C1, 150 and 170 ms for P1, and 220 and 240 ms for P2 for electrodes PO3, PO4, POz, O1, O2, Oz, and Iz.

Object Masking Task.. A backward-masking task using common household objects as targets[43] was administered during the interval after HFS in the task described above. The task was run in E-Prime (Psychology Software Tools, Inc). All stimuli were presented on an Asus V0236 LCD 23-inch monitor running at a refresh rate of 75 Hz. All stimuli measured 3.6° × 3.6° of visual angle. Target stimuli from 1 of 6 different object categories were presented for 13.33 ms. Target stimuli were followed by a masking stimulus (overlapping black and white curved lines) that was presented for 55.33 ms after a variable interstimulus interval (ISI) from 13.33 to 146.67 ms (in 13.33 ms increments), for a total of 8 ISIs. There were 12 trials per ISI, plus 12 unmasked trials. After each trial, a list of the 6 object categories appeared and participants verbally reported which object they saw, and the tester entered the response into the computer. Because participants gave verbal responses, reaction times were not recorded. The dependent measure was the number of correct responses averaged over ISIs of 40 to

Table 1. Demographics and Clinical Characteristics of the Sample.

	Schizophrenia (n = 27)
Gender, male, % male	67
Age, years, mean (SD)	47.70 (9.13)
Race, %	
Black	41
White	52
Other	7
Ethnicity, Hispanic/Latino, %	19
Education, years, n (%)	13.15 (1.75)
Parental education, years, n (%)	13.52 (2.93)
Illness duration, years, mean (SD)	24.0 (11.56)
Total hospitalizations, mean (SD)	5.31 (7.0)
BPRS total, mean (SD)	37.18 (11.21)
SANS total, mean (SD)	30.91 (17.61)
RFS total, mean (SD)	17.26 (4.66)

Abbreviations: BPRS, Brief Psychiatric Rating Scale; SANS, Scale for the Assessment of Negative Symptoms; RFS, Role Functioning Scale.

93.33 ms. We chose these middle ISIs as they consistently showed masking effects whereas the lowest and highest ISIs showed floor and ceiling effects, respectively.

Statistical Analyses

To examine the effects of tDCS on patients' object masking performance and visual LTP VEPs, we used the general linear mixed model (GLMM), which allows us to include all available data from all subjects in the analyses. For object masking, our model included tDCS condition (anodal, cathodal, sham) and SOA (middle 4 SOAs) as within-subject factors, and the tDCS condition by SOA interaction. For each of the 3 VEPs, our model included the following factors: HFS (pre, post), input specificity (tetanized, nontetanized), and tDCS condition (anodal, cathodal, sham), as well as the 2- and 3-way interaction terms. We were primarily interested in the HFS by tDCS condition interaction, and whether any observed effects of tDCS stimulation on the HFS plasticity effect were input specific. For relevant follow-up tests, we calculated Cohen's *d* effect sizes.

Results

Demographic and Clinical Characteristics

The sample was two-thirds male with a mean age of 48 years and mean illness chronicity of 24 years (see Table 1). Twenty-three of the 27 participants were receiving atypical antipsychotic medications, 1 typical antipsychotic medication, 2 not taking antipsychotics, and 1 was missing medication information. The procedures were well-tolerated, with the most commonly reported side effects associated with stimulation being slight burning sensations, itchiness, warmth, and fatigue.

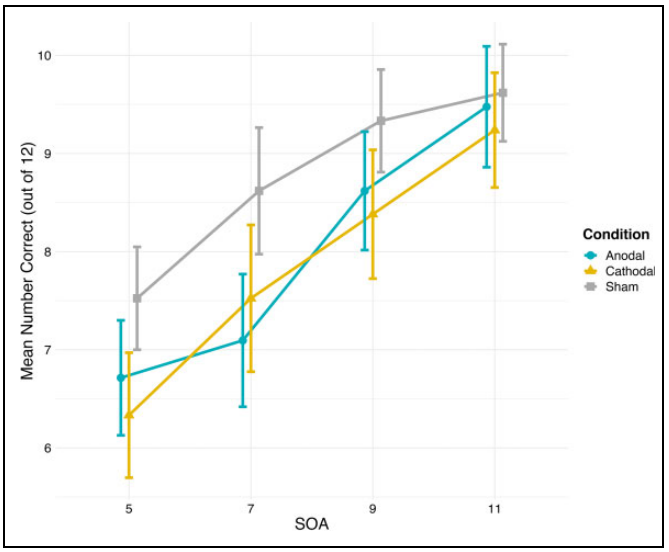

Figure 1. Behavioral effects of transcranial direct current stimulation (tDCS) on object masking showing poorer performance in both cathodal (yellow line) and anodal (blue line) tDCS conditions compared with sham (gray line). Bars represent ±1 standard error.

Effects of tDCS on Object Masking

We excluded 3 subjects from the object masking data analysis due to poor performance (less than 50% correct) on the unmasked trials. There was a significant main effect of SOA, $F(1, 239.42) = 115.01$, $P < .001$. As expected, object recognition improved in all tDCS conditions as SOA increased. There was also a significant main effect of tDCS condition, $F(2, 239.97) = 3.79$, $P = .02$. Compared with sham, both anodal ($P = .02$) and cathodal ($P = .01$) stimulation significantly worsened performance across SOAs (Figure 1); there was no difference in performance between the anodal and cathodal conditions. The SOA × tDCS condition interaction was not significant, $P = .46$.

Effects of tDCS on Visual Neuroplasticity

For C1, the analyses revealed no significant main effects of tDCS condition, input specificity, or HFS, as well as no significant interactions.

For P1, there were significant main effects of tDCS condition, $F(2, 274.69) = 4.21$, $P = .02$, and input specificity, $F(1, 274.07) = 6.71$, $P = .01$. P1 amplitude was larger in the anodal ($P = .03$, $d = 0.31$) and cathodal ($P = .01$, $d = 0.40$) conditions compared to sham. There was a main effect for a larger response for nontetanized ($M = 2.27$; SD = 2.65) compared with tetanized stimuli ($M = 1.84$; SD = 2.65), $d = 0.33$. However, there were no significant interactions, and HFS did not affect amplitudes.

For P2, there was a significant main effect of input specificity, $F(1, 273.99) = 5.49$, $P = .02$, with a larger response for nontetanized ($M = 1.86$; SD = 1.77) compared with tetanized stimuli ($M = 1.51$; SD = 1.77) across pre- and post-HFS, $d =$

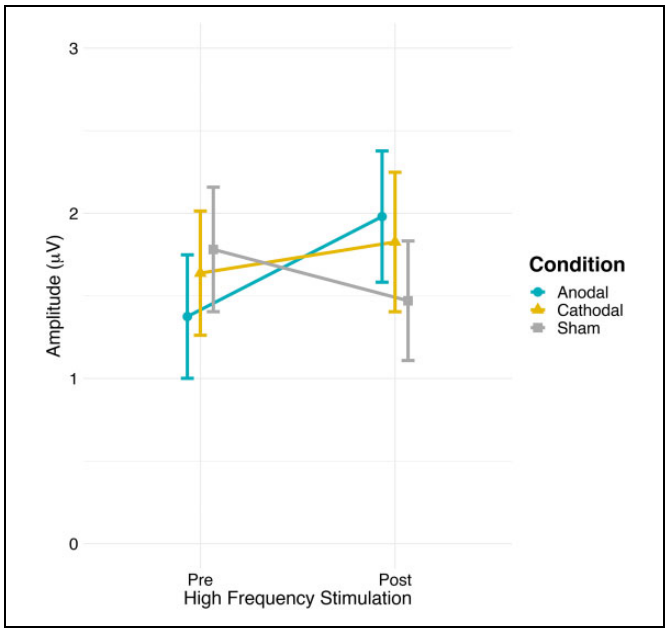

Figure 2. Non–input-specific high-frequency stimulation (HFS) by transcranial direct current stimulation (tDCS) interaction for the P2 visual evoked potential (VEP) component showing an increased amplitude post-HFS versus pre-HFS in the anodal condition (blue line), but no significant differences for cathodal (yellow line) or sham (gray line) stimulation. Bars represent ± I standard error.

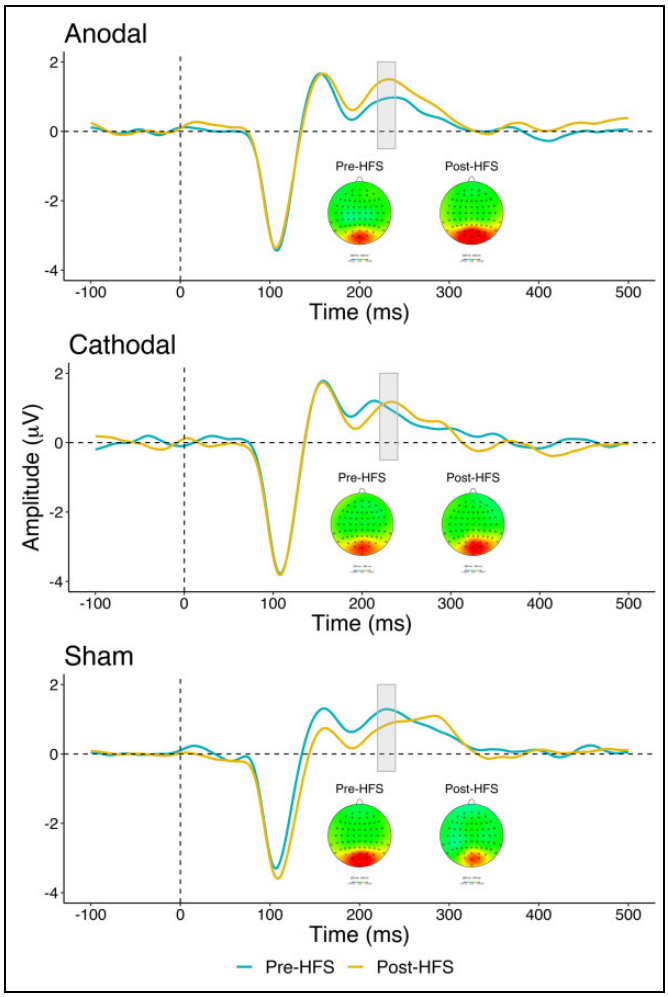

Figure 3. Grand average waveforms (averaged over electrodes PO3, PO4, POz, O1, O2, Oz, and Iz) and topographical maps for P2 activity (in the 220-240 ms time window, highlighted by the gray box) pre–high-frequency stimulation (HFS) (green line) and post-HFS (yellow line). Non–input-specific plasticity effects are apparent only with anodal transcranial direct current stimulation (tDCS) (top), with larger amplitudes post- versus pre-HFS. No significant effects were seen for cathodal (middle) or sham (bottom) stimulation conditions.

0.31. Also, we found a significant non–input-specific HFS by tDCS condition interaction, $F(2, 273.99) = 3.08$, $P = .047$ (Figure 2). Follow-up contrasts revealed that for the anodal condition only, P2 amplitude was significantly modulated (ie, more positive) post- versus pre-HFS ($M = 1.98$; SD = 2.06 vs $M = 1.37$; SD = 1.94), $F(1, 273.99) = 5.60$, $P = .02$, $d = 0.53$. There were no differences in pre- versus post-HFS in either the cathodal ($d = 0.19$) or sham conditions ($d = 0.30$). Figure 3 shows the P2 grand averages and topographical maps pre- and post-HFS for each tDCS condition.

Given that tDCS was administered prior to the EEG session, it is possible that stimulation could have caused changes to P2 VEPs at baseline, prior to HFS. Those VEPs in turn may have returned to "baseline" levels 30 to 36 minutes after HFS, which could be mistaken for a true LTP effect. We therefore analyzed if there were effects of tDCS condition on the average of the 2 baseline sessions by conducting a 1-way repeated-measures analysis of variance on pre-HFS P2 amplitudes, with condition as the within-subject variable. While the condition effect was not significant, $F(2, 48) = 0.92$, $P = .407$, follow-up contrasts revealed a trend difference between anodal and sham amplitudes, $P = .063$.

Discussion

In this study, we evaluated the behavioral and neurophysiological effects of tDCS applied to the visual cortex in people with schizophrenia. We specifically examined whether active tDCS affects backward masking of objects and amplitude of VEP components in a visual LTP paradigm. A single session of tDCS over the central occipital lobe (Oz) worsened performance on a task of object processing in that anodal and cathodal stimulation reduced masking performance compared with sham. The EEG data showed significant modulation of LTP effects in only one VEP component: the amplitude of P2, averaged over tetanized and nontetanized stimuli, was significantly larger after HFS than before with anodal tDCS. Taken together, our performance-based findings show that a single session of neurostimulation over the occipital cortex appears to modulate behavior on an early visual processing task. However, the neurophysiological results are specific to one

waveform and one stimulation condition and, hence, do not allow for a confident interpretation.

Our behavioral results are similar to those of a separate study, which also found that tDCS (over the left dorsolateral prefrontal cortex) worsened visual attention in schizophrenia.[44] However, our results are inconsistent with two separate studies of face and object processing in healthy individuals: one found that anodal tDCS over the right occipital cortex improved perception and memory,[45] whereas the other found that cathodal tDCS had no overall effect on processing.[46] Our finding that a single dose of tDCS disrupts visual perception in schizophrenia raises the question of whether multiple sessions are needed to produce a beneficial effect. For instance, a study that administered multiple sessions of tDCS to the left lateral occipital cortex during an object recognition task found that anodal tDCS improved perceptual learning (over 4 days) in healthy individuals.[47] However, in another study that used repeated stimulations, anodal tDCS applied to Oz impaired the overnight consolidation of learning on a visual contrast detection task.[48]

Another possibility as to why we found worsening of performance could be because the effects of tDCS tend to decay faster for the visual cortex than for other cortical areas.[49] Thus, it might have been more beneficial for our subjects to receive stimulation during, not before, the backward masking task. Nevertheless, studies in healthy subjects show that online stimulation is not always more effective. For example, one study of visual processing (using an orientation discrimination task) found that anodal stimulation before the task yielded larger effects than online stimulation.[50] This pattern was confirmed in a separate study of face/object processing in which improvement was weaker or absent when tDCS was applied online versus offline.[45]

Regarding our EEG findings, we did not find any effects on the C1. We found an overall effect of tDCS on P1 amplitudes averaged over pre- and post-HFS. The results suggest that tDCS does indeed influence an electrophysiological component of early visual processing, but not in a way that reflects classical Hebbian LTP. We found non–input-specific plasticity of the P2 response during anodal stimulation; classic Hebbian LTP would be reflected by input-specific effects, not general effects to all visual stimuli. While the findings with the P2 are consistent with the theory that anodal stimulation increases cortical neuroplasticity, these results need to be interpreted with caution for a couple of reasons. First, the finding of neuroplasticity occurred with only one waveform and one type of stimulation, and it does not survive correction for multiple comparisons. Second, it is possible that the anodal tDCS affected the pre-HFS amplitude of P2, given that we found a trend in that direction compared with the sham condition ($P = 0.06$). Therefore, this study did not provide strong or consistent support for effects of tDCS on LTP-like neuroplasticity.

There were a few limitations to our study. First, we administered tDCS prior to the EEG and behavioral tasks. Regarding EEG, as mentioned above, this aspect of the design may have affected neural responses prior to administering HFS, rather than having an effect on plasticity effects after HFS. Similarly, given that up to 20 minutes passed between the end of tDCS and the beginning of the EEG recordings. This 20-minute window added to the total length of the EEG session and may have led to a diminished effect of tDCS. It may be more effective to administer tDCS simultaneously with the tetanizing stimulus in the plasticity task (and not during the pre- or post-tetanus assessments) to minimize the effect of tDCS on the VEP baseline amplitudes and to mitigate any potential decay of tDCS effects. Second, we have previously reported that the reliability of VEP change scores, like those used in the current study, is poor while the reliability of the raw VEP amplitudes is very high.[29] This issue of reliability might potentially explain our findings of a general effect of tDCS on P1 amplitudes as those are a more reliable measurement than the change scores we calculated to examine for plasticity effects. Finally, most participants were taking antipsychotic medications and those could have influenced the pattern of results.

In summary, we found detrimental effects of tDCS, both anodal and cathodal, on a behavioral visual processing task. However, we did not find any evidence of an input-specific plasticity effect and an inconsistent effect of tDCS delivered prior to visual stimulation on plasticity in people with schizophrenia. The reason for the lack of stimulation effects on plasticity may be because tDCS was not delivered simultaneously with the tetanizing visual stimulus. While neurostimulation may influence early visual processing, the present findings, combined with the inconsistency of therapeutic effects reported in studies of healthy individuals, emphasize the need for more research on the relevant parameters for stimulation of visual processing regions in clinical populations.

Author Contributions

CJ contributed to conception and design; contributed to acquisition, analysis, and interpretation; drafted manuscript; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy. JKW contributed to design; contributed to acquisition, analysis, and interpretation; drafted manuscript; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy. BJR contributed to design; contributed to analysis and interpretation; drafted manuscript; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy. DHM contributed to design; contributed to analysis and interpretation; drafted manuscript; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy. MFG contributed to conception and design; contributed to interpretation; drafted manuscript; critically revised manuscript; gave final

approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

Declaration of Conflicting Interests

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ORCID iD

Jonathan K. Wynn https://orcid.org/0000-0002-1763-8540

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