

## Effect of Transcranial Direct Current Stimulation on Prefrontal Inhibition in Schizophrenia Patients with Persistent Auditory Hallucinations: A Study on Antisaccade Task Performance

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### ABSTRACT

**Background:** Deficient prefrontal cortex inhibitory control is of particular interest with regard to the pathogenesis of auditory hallucinations (AHs) in schizophrenia. Antisaccade task performance is a sensitive index of prefrontal inhibitory function and has been consistently found to be abnormal in schizophrenia. **Methods:** This study investigated the effect of transcranial direct current stimulation (tDCS) on antisaccade performance in 13 schizophrenia patients. **Results:** The tDCS resulted in significant reduction in antisaccade error percentage ( $t = 3.4$ ;  $P = 0.005$ ), final eye position gain ( $t = 2.3$ ;  $P = 0.042$ ), and AHs severity ( $t = 4.1$ ;  $P = 0.003$ ). **Conclusion:** Our results raise the possibility that improvement in antisaccade performance and severity of AH may be mechanistically related.


**Key words:** Antisaccade, hallucinations, schizophrenia, transcranial direct current stimulation

### INTRODUCTION

Executive function deficits are widely understood to be a core aspect of schizophrenia. Among the several deficits studied till date, deficient prefrontal cortex (PFC) inhibitory control is of particular interest with regard to the pathogenesis of auditory hallucinations

(AHs) in schizophrenia. An association between deficient prefrontal inhibition and AH in schizophrenia has been suggested by several authors.<sup>[1,2]</sup> Recent work in this underexplored area has shown specific links between AH and inhibition deficit that correlate with the severity of AH.<sup>[3]</sup> Contextually, antisaccade task performance is understood to be a sensitive index of prefrontal inhibitory function and has been consistently found to be abnormal in schizophrenia patients.<sup>[4]</sup> Results obtained by our group suggest a significant positive correlation between AH severity and antisaccade error percentage (manuscript under review).

Transcranial direct current stimulation (tDCS) is a safe and noninvasive brain stimulation method for selectively modulating cortical excitability.<sup>[5]</sup> It causes polarity

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specific changes in excitability; anodal current increases cortical excitability, whereas cathodal stimulation causes a decrease and is emerging as a novel modality for treating resistant AH in schizophrenia patients.<sup>[6]</sup> Given the evidence that anodal tDCS over dorsolateral PFC (DLPFC) enhances executive functions in healthy subjects,<sup>[7,8]</sup> one may hypothesize that it may also correct deficient prefrontal inhibitory control and thus improve antisaccade performance. Interestingly, a recent study has found a decrease in antisaccades error rate in healthy controls following anodal tDCS.<sup>[9]</sup> Pursuing this further, in the present study, we examined the effect of add-on tDCS on antisaccade task performance in schizophrenia patients ( $n = 13$ ) with persistent AH despite adequate antipsychotic treatment. We hypothesized that following tDCS the number of errors in the antisaccade task will decrease. We further hypothesized that improvement in antisaccade task performance will be accompanied by a decrease in the severity of AH.

## MATERIALS AND METHODS

### Participants

Patients attending the clinical services of the National Institute of Mental Health and Neurosciences (India), who fulfilled Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (DSM-IV) criteria for schizophrenia with persistent AH (defined as psychotic symptom rating scales [PSYRATS] AH sub-scale<sup>[10]</sup> items of frequency, duration, and disruption each having a score  $\geq 2$  despite treatment with adequate antipsychotic dosage for at least 3-month) were examined in this study. All patients were right eye dominant as ascertained using the hole-in-the-card test and were on a stable dose of oral antipsychotic medications. The diagnosis of schizophrenia was established using Mini International Neuropsychiatric Interview Plus — DSM-IV version,<sup>[11]</sup> concurred by two psychiatrists through independent clinical interviews. None of the patients had:

1. Alcohol abuse/dependence,
2. Neurological/medical disorder,
3. Developmental delay/mental retardation.

### Clinical assessment

The severity of AH was measured using the AH subscale of PSYRATS.<sup>[10]</sup> The AH severity ratings and eye tracking experiments were done at baseline on the 1<sup>st</sup> day before starting tDCS as well as on the 5<sup>th</sup> day after the completion of tDCS. Ratings were not available for three subjects. After complete description of study to the subjects, written informed consent was obtained. The study was approved by the Institute's Ethics Committee.

### Eye tracking methodology: Antisaccade task

Eye movement recordings were conducted in a room

with controlled luminance. Stimuli were displayed on a 22-inch flat screen monitor (FuzHion, Viewsonic, 120 Hz) placed 74.3 cm in front of the subject. Eye tracking data were collected using an EyeLink 1000 eye-tracker (SR Research, Canada) sampling at 1000 Hz. Head movements were constrained using chin rest and forehead abutments. The saccadic task was based on the principles and procedures as described earlier.<sup>[12]</sup> Each participant performed a total of 24 prosaccade and 48 antisaccade trials. The stimuli for each trial appeared on a screen with a black background. The fixation stimulus and the target stimulus comprised of a circle (green in color for prosaccade, red in color for antisaccade) of 0.3 cm diameter. Each trial began with the circle located at the center of the screen, for a random duration (between 800 and 1200 ms). After this random interval, the central fixation stimulus disappeared and following a 200 ms gap, the target stimulus appeared. This target appeared at 4 possible locations,  $\pm 6^\circ$  and  $\pm 12^\circ$  from the center. The instruction to the subject for the prosaccade task was to look at the target when it appeared, and that for the antisaccade task was to look at the mirror image location of the target without looking at the target itself.

### Transcranial direct current stimulation procedure

Transcranial direct current stimulation was given using a standard equipment (Neuroconn DC Stimulator Plus, [http://www.neuroconn.de/dc-stimulator\\_plus\\_en/](http://www.neuroconn.de/dc-stimulator_plus_en/)) as per previous description<sup>[6]</sup> with stringent safety measures.<sup>[13]</sup> The anode was placed over a point midway between F3 and FP1 (left DLPFC) and the cathode located over a point midway between T3 and P3 (left temporo-parietal junction [TPJ]). The electrodes size was 35 cm<sup>2</sup> and the stimulation level was set at 2-mA for 20 min. The sessions were conducted twice a day (separated by at least 3-h) for 5 consecutive days;<sup>[6]</sup> none of the patients reported any significant adverse effect.<sup>[13]</sup>

### Analysis of eye tracking data

Saccades with latencies  $< 80$  ms and  $> 600$  ms after target onset were excluded from analysis as anticipations or delayed responses due to the subject not paying enough attention. The performance measure of specific interest in this study was the antisaccade error percentage (percentage of analyzable antisaccade trials in which the first saccade following target onset went toward, rather than away from the target). We also conducted exploratory analyses on other antisaccade performance parameters including latency and amplitude gain of correct antisaccades, peak velocity of correct antisaccades, final eye position gain (ratio of final eye position to correct eye position), and analogous measures for the prosaccade task.

## Statistical analysis

The demographic and clinical characteristics were examined using descriptive statistics. After ascertaining normality of data distribution using Shapiro–Wilk test, statistical analyses were done using paired samples *t*-test (R version-3.1.1; <http://www.R-project.org/>).

## RESULTS

Thirteen patients were assessed in this study. (Age =  $29.6 \pm 8.1$  years; male:female = 4:9, duration of illness =  $7.8 \pm 5.7$  years) chlorpromazine equivalence of their antipsychotic medication was  $779.2 \pm 562.2$  mg/day. Antipsychotic medication details (number in parentheses represent number of patients on each medication, five patients were on more than one antipsychotic): Clozapine-(6), haloperidol-(3), aripiprazole-(3), risperidone-(2), iloperidone-(2), amisulpride-(1), olanzapine-(1).

Following tDCS, there was a significant reduction in antisaccade error percentage (baseline:  $80.0 \pm 10.7$ ; follow-up:  $69.7 \pm 17.8$ ;  $t = 3.4$ ;  $df = 12$ ;  $P = 0.005$ ) [Figure 1a] and final eye position gain (baseline:  $1.3 \pm 0.6$ ; follow-up:  $0.9 \pm 0.4$ ;  $t = 2.3$ ;  $df = 12$ ;  $P = 0.042$ ). Concurrently, there was a significant reduction in the severity of AH (baseline:  $30.6 \pm 3.6$ ; follow-up:  $18.6 \pm 8.7$ ;  $t = 4.1$ ;  $df = 9$ ;  $P = 0.003$ ) [Figure 1b]. No statistically significant change was observed in any other antisaccade or prosaccade parameter [Supplementary Table 1].

## DISCUSSION

The principal study finding was that tDCS resulted in a significant reduction in antisaccade error percentage and AH severity. Antisaccade errors are generally thought to be due to the inability to

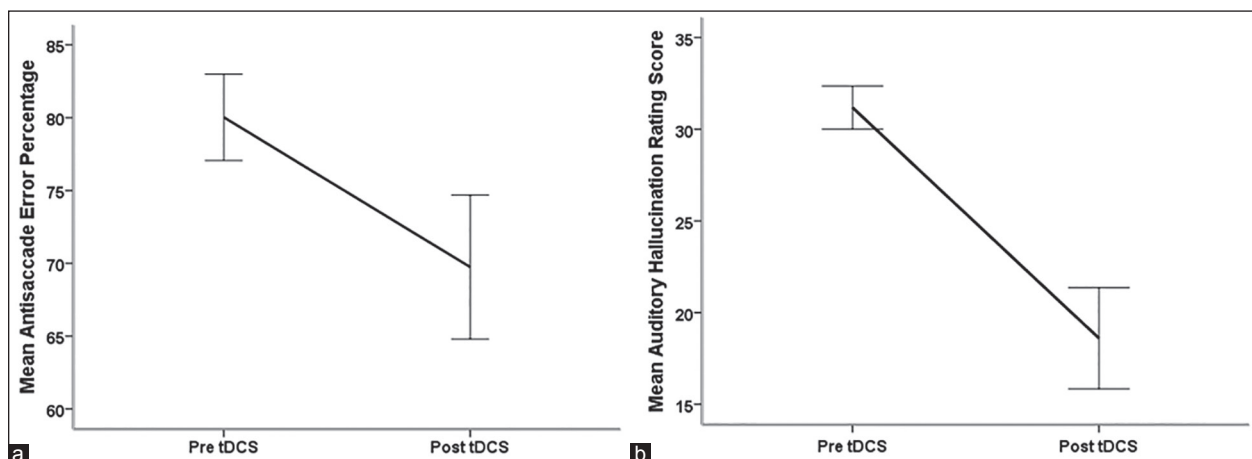
suppress prepotent pro-saccadic response toward the target, which is understood to be PFC mediated.<sup>[1]</sup> Hence, our findings indicate that tDCS might have improved prefrontal inhibitory control potentially due to increased PFC activity consequent to anodal stimulation.

The mechanism of action of tDCS that underlies AH improvement is poorly understood. Both TPJ hyperactivity and deficient frontal inhibition resulting in dysfunctional frontotemporal connectivity have been implicated in its pathophysiology. It has been suggested that improvement in the severity of AH could be due to a correction of one or both of these abnormalities.<sup>[6]</sup> Concurrent improvement in antisaccade performance and severity of AH following tDCS probably indicates

**Supplementary Table 1: Eye tracking performance parameters (mean  $\pm$  SD) before and after add-on tDCS**

Parameter	Pre-tDCS	Post-tDCS	<i>t</i>	<i>P</i>
<b>Antisaccade task</b>				
Error percentage	80.0 $\pm$ 10.7	69.7 $\pm$ 17.8	3.4*	0.005
First correct saccade latency (ms)	336.4 $\pm$ 62.9	363.0 $\pm$ 116.6	-0.6	0.5
First correct saccade amplitude gain	1.1 $\pm$ 0.8	1.1 $\pm$ 0.5	0.3	0.7
First correct saccade peak velocity (degrees/s)	271.1 $\pm$ 96.4	329.8 $\pm$ 120.4	-1.2	0.3
Final eye position gain	1.3 $\pm$ 0.6	0.9 $\pm$ 0.4	2.3*	0.042
<b>Prosaccade task</b>				
Error percentage	3.0 $\pm$ 5.5	2.4 $\pm$ 4.0	0.4	0.6
First correct saccade latency (ms)	159.0 $\pm$ 34.1	155.2 $\pm$ 26.8	0.5	0.6
First correct saccade amplitude gain	1.0 $\pm$ 0.2	1.0 $\pm$ 0.2	-0.1	0.9
First correct saccade peak velocity (degrees/s)	305.0 $\pm$ 49.1	310.0 $\pm$ 56.5	-0.4	0.7
Final eye position gain	0.9 $\pm$ 0.2	0.9 $\pm$ 0.2	-0.6	0.6

\**P* < 0.05. tDCS — Transcranial direct current stimulation; SD — Standard deviation



**Figure 1:** Significant change in antisaccade error percentage (a) and auditory hallucination rating score (b) following add-on treatment with transcranial direct current stimulation in schizophrenia patients

that correction of prefrontal inhibition deficits may be mechanistically related with decrease the severity of AHs. This study, however, did not test this hypothesis directly and hence, it is difficult to dissect these effects out. Future studies may look at different montage placements to elucidate the mechanistic specificity better.

There was a significant decrease in final eye position gain following tDCS. While prior to tDCS subjects overshoot the target location (mean gain >1), following tDCS their final eye position was closer to the target location. Parietal cortex is known to be important for the processing of spatial data in the context of antisaccades<sup>[14]</sup> and it is likely that the finding is a manifestation of cathodal stimulation of the TPJ leading to decrease in excitability of the parietal cortex.

The significant limitations of this study are the small sample size, open-label study design, and the lack of a control arm with sham tDCS. The possibility of practice effect cannot be ruled out and remains a major limitation of the study.<sup>[15]</sup> Further, antipsychotic drugs that the subjects were on can potentially influence findings due to their effects on the oculomotor system. However, since the patients were on stable prescription for at least 2 months prior and medications were not changed during the study, this is unlikely to a major confounding factor. Lack of comprehensive characterization of other positive and negative symptoms is another limitation. However, given the unexplored nature of the subject under consideration, such open-label observations merit consideration as they offer potential leads for further research.

The novel observation of this study is that anodal tDCS may help in correcting deficits in antisaccade task performance in patients with schizophrenia. The study also raises the possibility that improvement in antisaccade performance and severity of AH may be mechanistically related. This link can be explored in future studies in a large sample of subjects using a randomized, double-blind, sham-controlled design.

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