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Letter to the Editor

Effect of fronto-temporal transcranial direct current stimulation on corollary discharge in schizophrenia: A randomized, double-blind, sham-controlled mediation analysis study☆

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To the Editor:

Deficient corollary discharge (CD) has been linked to agency related anomalies in schizophrenia (SCZ) (Poletti et al., 2017), especially with pathophysiology of auditory verbal hallucination (AVH) (Heinks-Maldonado et al., 2007). Transcranial Direct Current Stimulation (tDCS), a non-invasive, safe neuromodulation technique, is a re-emerging intervention (Brunoni et al., 2012) with promising potential to treat schizophrenia (Mondino et al., 2015a). In an open label study, we reported add-on tDCS to ameliorate CD deficit in SCZ patients with persistent AVH (Nawani et al., 2014). In this report, 1) we replicate this observation using a randomized, double-blind, parallel-arm, sham-controlled design in an independent sample of SCZ patients, and 2) explore the role of amelioration of CD deficit as mechanistic basis of tDCS action through mediation analysis.

Thirteen DSM-IV-TR SCZ patients with persistent AVH were examined in this study with written informed consent as approved by the ethics committee [Trial No. CTRI/2014/12/005307]; these patients are a random subset of a previous clinical study (Bose et al., 2018) who underwent neurophysiological assessment of CD at pre and post tDCS time points. Using an auditory paradigm (Ford et al., 2010; Nawani et al., 2014), N1 component of event-related potential that reflects cortical responsiveness of auditory cortex to sounds, was elicited in two conditions – i) Talk (with online auricular feedback of self-spoken speech sounds) and ii) Listen (passive playback of recorded self-spoken speech sounds). The attenuated N1 amplitude of talk condition relative to listen condition denotes cortical suppression during talk and is indicative of successful corollary discharge. N1 suppression, i.e. degree of cortical suppression or corollary discharge index (CDI) was calculated by subtracting Listen condition N1 amplitude from Talk condition N1 amplitude. EEG data was collected from midline electrodes (10–20 system). N1 amplitudes from CZ as well as FCZ were analyzed separately.

The SCZ patients received twice-daily, 20-minute sessions of fronto-temporal verum or sham tDCS for 5 consecutive days in a randomized, double-blind sham-controlled design. Anode was placed at left dorsolateral prefrontal cortex (DLPFC) and cathode was placed at left temporo-parietal junction (TPJ). In verum tDCS condition, a constant current of 2 mA was delivered for 20 min with additional ramp-up and ramp-down phase of 20 s each at the beginning and end of the session respectively. During the sham tDCS, current was delivered at 2 mA strength for the first 40 s; this resulted in a short period of skin sensations similar to that of active/verum stimulation. After 40 s of stimulation, only a small current pulse was delivered every 550 ms (110-μA over 15 ms with peak current lasting for 3 ms). Randomization, blinding, and tDCS procedures were performed with stringent safety criteria as per previous descriptions (Bose et al., 2018). Clinical assessment and neurophysiological assessment of corollary discharge were done at pre-RCT and post-RCT time points.

The verum and sham tDCS groups were comparable on important socio-demographic/clinical parameters [Table 1]. At post-RCT time point, significantly greater percentage reduction in AVH severity was seen in verum (32.24 ± 16.47) compared to sham (4.78 ± 8.84) tDCS group ($t = 3.64$, $p = 0.004$). Prior to tDCS treatment, N1 amplitudes (μV) (at CZ) from Talk and Listen conditions did not differ significantly from each other, indicating inadequate corollary discharge in both verum [Pre-tDCS N1 amplitude (μV) | Talk: −2.04 ± 2.13; Listen: −1.56 ± 0.67; $p = 0.61$] and sham [Pre-tDCS N1 amplitude (μV) | Talk: −1.66 ± 1.04; Listen: −1.52 ± 2.80; $p = 0.75$] tDCS groups. Following treatment with add-on tDCS, in verum group, significant difference was observed between N1 amplitudes from Talk and Listen conditions [Post-tDCS N1 amplitude (μV) | Talk: −1.12 ± 0.82; Listen: −1.88 ± 0.81; $z = 2.19$, $p = 0.028$]; however, this was not observed in the sham group [Post-tDCS N1 amplitude (μV) | Talk: −2.02 ± 1.68; Listen: −2.10 ± 1.53; $z = 0.31$, $p = 0.753$]. Percent change in CDI (at FCZ) positively correlated with percent change in AHRS from pre-RCT to post-RCT time-point for the entire sample ($N = 13$; $\rho = 0.55$, $p = 0.05$).

To explore this correlation, mediation analysis (Preacher and Hayes, 2004) was modelled with tDCS type (Verum vs. Sham) as independent variable, percent change in AVH severity as dependent variable and percent change in CDI (at FCZ) as the mediator. Result indicated tDCS type (verum/sham) to be a significant predictor of percent change in AVH severity: ($\beta = -27.46$, $p = 0.003$) as well as of percent change in CDI ($\beta = -1.40$, $p = 0.033$). Percent change in CDI turned out to be a significant predictor of percent change in AVH severity ($\beta = 8.87$, $p = 0.014$). However, when controlled for percent change in CDI, tDCS type ceased to be a significant predictor of percent change in AVH severity ($\beta = -15.0$, $p = 0.063$). Approximately, 75% of the variance ($R2 = 0.756$, $p < 0.001$) was accounted for by the predictors. As recommended for small samples, bootstrap estimation approach with 5000 samples was used to examine the indirect effect of independent variable on dependent variable through proposed mediator for significance. The coefficient of indirect

☆ The findings of this study have been presented at - 1) 2nd International Brain Stimulation Conference, NH Hesperia Towers, Barcelona, Spain, 5th–8th March 2017 and 2) 6th Biennial Schizophrenia International Schizophrenia Research Society Conference, Florence, Italy, 4th–8th April 2018.

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Table 1
Baseline demographic & clinical characteristics of schizophrenia patients treated with verum tDCS (n = 7) and sham tDCS (n = 6).

Characteristic	Verum tDCS	Sham tDCS	Stats[a]	p
Age	33.71 ± 07.29	32.83 ± 07.19	t = 0.21	0.831
Sex (M/F)	6:1	3:3	$\chi 2 = 1.93$	0.164
Age at onset of illness (in years)	24.71 ± 07.40	22.33 ± 04.84	z = 0.64	0.517
Total duration of illness (in years)	09.00 ± 06.32	10.50 ± 03.93	z = 0.50	0.626
SAPS total score	35.29 ± 13.53	40.50 ± 10.65	t = 0.76	0.426
SANS total score	19.86 ± 12.06	30.00 ± 13.46	t = 1.43	0.179
AHRS total score	31.00 ± 05.35	30.17 ± 02.85	t = 0.34	0.740

SAPS - Scale for Assessment of Positive Symptom; SANS - Scale for Assessment of Negative Symptom; AHRS - Auditory Hallucination Rating Scale.
[a] t = Independent sample *t*-test; z = z value for Mann-Whitney *U* test; χ^2 = chi-square test.

effect was significant, $\beta = -12.46$, SE = 6.92, 95% CI = −31.20, −2.79, and significantly different from zero at $p < 0.05$ (two tailed).

In this study, only verum tDCS group showed improvement in CD function with concurrent reduction in AVH scores. In verum tDCS group, at post-RCT time point, attenuation in Talk condition N1 amplitude was noticed as the mean value of N1 Talk condition amplitude for the verum tDCS group became more positive indicating correction of CD deficit. Furthermore, change in CDI was not only found to correlate with change in AVH severity, but it also accounted for the effect of tDCS type (verum vs. sham) on treatment outcome (AVH severity) in a mediation analysis model. It has been postulated that due to deficient CD in SCZ patients, 'misperceived' internal speech attributed to external sources manifests as AVH (Heinks-Maldonado et al., 2007). Hence, similar to source monitoring amelioration (Mondino et al., 2015b), this study suggests that correction of the deficient CD might be one of the mechanisms underlying the beneficial effects of add-on fronto-temporal tDCS on AVH treatment in schizophrenia. This observation needs to be replicated in large sample.

Role of contributors

Author GVS designed the study. Authors AB, VSK, SMA, SS & VSS delivered the tDCS procedures & collected the data. Clinical symptom ratings were done by AB & VSK. Authors GV & JCN supervised the clinical assessment and ascertained the clinical ratings. Authors AB & HN acquired and analyzed the electrophysiology data under the supervision of DK. Authors AB& SVK performed the statistical analyses. Authors AB & GVS managed the literature search and wrote the first draft of manuscript. All authors revised and optimized further versions of the manuscript. All the authors have contributed to and have approved the final manuscript.

Conflict of interest

Conflict of interest – none.

All the authors assure that there are no commercial or financial involvements that might present an appearance of a conflict of interest in connection with this article.

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Anushree Bose
Hema Nawani
Sri Mahavir Agarwal
Venkataram Shivakumar
Sunil V. Kalmady
Sonia Shenoy
Vanteemar S. Sreeraj
Janardhanan C. Narayanaswamy
Devvarta Kumar
Ganesan Venkatasubramanian*

WISER Neuromodulation Program, Department of Psychiatry, National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore, India

*Corresponding author at: WISER Neuromodulation Program, Department of Psychiatry, National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore 560029, India.

E-mail addresses: gvs@nimhans.ac.in, venkat.nimhans@gmail.com (G. Venkatasubramanian).

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