Transcranial Direct Current Stimulation as an Add-On Intervention in Patient with Schizophrenia

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ABSTRACT

Introduction: Transcranial Direct Current Stimulation (tDCS) is a non-invasive form of neuromodulation that delivers a constant low amplitude electric current to the scalp via electrodes. This study examines the effectiveness of add-on tDCS on auditory hallucination and insight in subjects with chronic schizophrenia, who continued to have auditory hallucination despite adequate trials with first- and second-generation antipsychotic medication. Methods: Thirty-two subjects with chronic schizophrenia having medication refractory auditory hallucination were selected from a tertiary center. The participants included 23 males and 9 females, with a mean age of 35.41 yrs., and the mean illness duration of 12.91 yrs. tDCS was carried out using 2 mA direct current, for 20 mins for five successive days, with two sessions per day (total 10 sessions), with the anode placed over left dorsolateral prefrontal cortex (DLPFC) and the cathode over left temporo-parietal junction (TPJ), and assessment done using Positive and Negative Syndrome Scale (PANSS), Auditory Hallucination Rating Scale (AHRS) and Becks Cognitive Insight Scale (BCIS) on day 0, day 5 and day 30. Results: There was a significant improvement in auditory hallucination on AHRS, PANSS, positive symptom domain of PANSS, and P3 subscale of PANSS after 10 sessions, that is on day 5, but the effect weaned off by day 30. There was no significant change in the negative symptoms and insight over the study period. Conclusion: We report that add-on tDCS was effective for a brief duration in medication refractory auditory hallucination in patients with chronic schizophrenia. The effect was not sustained, suggesting that tDCS does not induce long-lasting neuroplasticity in the brain. There was no significant improvement in negative symptoms and insight. The study kindles the idea of maintenance tDCS for auditory hallucinations.

KEY WORDS

tDCS, auditory hallucination, schizophrenia

INTRODUCTION

Schizophrenia is one of the most burdensome mental disorders in terms of human suffering and societal expenditure (Chong, Teoh, Wu, 2016). It affects around 0.3-0.7% of people at some point in their lives (McGrath, Saha, Chant, Welham, 2008). Auditory verbal hallucinations (AVHs) are experienced by around 60-80% of people diagnosed with schizophrenia (Jablensky, 2010), out of which 25-30% of cases of auditory hallucinations who continued to have auditory hallucination despite adequate trials with first- and second-generation antipsychotic medication. But the outcome of tDCS studies have been inconsistent, as few studies fail to show any positive impact of tDCS in AVH (Fitzgerald et al., (2016); Smith et al., (2015); Frohlich et al., (2016)). The functional MRI brain study has demonstrated that active tDCS effects the resting-state functional connectivity of the left temporo-parietal junction in patients with Schizophrenia, that decreases the AVH severity (Mondino et al., (2016)).

The study aimed to investigate the add-on effect of tDCS in refractory auditory verbal hallucinations and insight. We took the null hypothesis, that there is no impact of add-on tDCS on auditory hallucination in patients with chronic schizophrenia receiving adequate pharmacological treatment. We also assessed the maintenance of the effect of tDCS on these hallucinations over one-month follow-up period.

METHODOLOGY

Patients were selected from department of psychiatry, PGIMER & Dr. Ram Manohar Lohia Hospital, New Delhi. Patients (n = 32) fulfilling ICD-10 criteria for schizophrenia, who continued to have auditory hallucination despite adequate pharmacological treatment for a duration of at least 3 months. Written informed consent was taken from each patient and his/her primary caregiver. The course of pharmacotherapy was not...
changed. Patients with co-morbid neurological illness, drug dependence, chronic skin disease of scalp and pregnancy were excluded.

Clinical assessment was done using PANSs scale, Auditory Hallucination Rating Scale (AHRs) and Becks cognitive insight scale (BCIS) at baseline. The scales were repeated after 10 sessions of tDCS and further three weeks. Each participant received tDCS, twice a day, with at least 3 hours gap for 5 days, total 10 sessions, with stimulation at 2 mA. The electrode placement was done using 10-20 montage. The anode was kept at the middle of the electrode over a point midway between F3 and FP1 (left dorsolateral prefrontal cortex) and the cathode placed over a point midway between T3 and P3 (left temporo-parietal junction). Each session was of 20-minute duration. Patients were asked to report any adverse effect during the session. The study was underta-ken after receiving approval from the institutional review board.

RESULT

We had 32 patients with schizophrenia, 23 males and 9 females, with a mean age of 35.41 yrs., and the mean illness duration of 12.91 yrs. The scores of AHRs decreased from 34.95 + 0.68 at Day 0 to 33.13 + 0.68 after 5 days of tDCS stimulation. The mean reduction in AHRs at day 5, compared to baseline was 1.47 ± 0.37, effect size = 3.93 (p value < 0.01) implying a significant effect, however the benefit was not sustained and not significant on day 30, with a mean reduction of 0.31 ± 0.37 (p = 0.68). The PANSS scores decreased from 65.66 ± 2.16 at baseline to 63.51 ± 2.16 on day 5 and then increased back to 65.22 ± 2.16 on day 30. Compared to AHRs, the response in PANSS is slow (slower response and slower rise), possibly as PANSS measures both domains - positive and negative symptoms.

This study reports significant correlation between improvement in AHRs and the duration of illness (rs = -0.49, p = 0.004) and also negative correlation between improvement in AHRs and the total baseline PANSS score of patients (rs = -0.69, p = 0.001), no significant side effect was reported by any participant.

DISCUSSION

The present study was undertaken to examine the effect of add-on tDCS on auditory hallucination and insight in the patients with chronic schizophrenia, having refractory auditory hallucinations despite adequate pharmacological treatment.

This study included a total of 32 patients with schizophrenia, 23 males and 9 females, with a mean age of 35.41 yrs, and the mean illness duration of 12.91 yrs. Each participant received 2 sessions of tDCS per day for 5 consecutive days after baseline assessment.

The sample size here is comparable to earlier studies (Smith et al., 2015; Brunelin et al., 2012; Frohlich et al., 2016). We used the fronto-temporal-parietal electrode placement protocol, which was used in earlier studies (Brunelin et al., 2012; Fitzgerald et al., 2014; Mondino et al., 2016; Bose et al., 2017; and Chang et al., 2018). The anode at the left dorsolateral prefrontal cortex (DLPFC) and cathode was placed at left temporo-parietal junction (TPI). This placement of tDCS can be supported by the meta-analysis by Jardari, Pouchet, Pins et al. (2011) which states that experiencing AVHs is linked with increased activity in fronto-temporal areas involved in speech generation and speech perception. This protocol of placement is also supported by the study by Mondino et al. (2016), in which functional MRI brain was done, which demonstrated that active tDCS reduced resting state functional connectivity (rs-FC) of the left TPI with the left anterior insula and the right inferior frontal gyrus and increased rs-FC of the left temporo-parietal junction with the left angular gyrus, the left dorsolateral prefrontal cortex and the precuneus. The reduction of AVH severity was linked with the reduction of the rs-FC between the left TPI and the left anterior insula (Mondino et al., 2016).

Effect of tDCS on auditory hallucination-

In the present study, AHRs scores decreased from 34.59 ± 0.68 at Day 0 to 33.13 ± 0.68 after 5 days of tDCS stimulation. The mean reduction in AHRs at day 5, compared to baseline was 1.47 ± 0.37, effect size = 3.93 (p value < 0.01) implying a significant effect, however the benefit was not sustained and not significant on day 30, with a mean reduction of 0.31 ± 0.37 (p = 0.68).

Compared to our results, in the study by Brunelin et al. (2012), the mean AHRs scores reduced from 28.3 (4.1) to 19.9 (5.8) in the tDCS group after 5 days, significantly larger than that in the sham group [from 27.6 (6.9) to 25.1 (7.7)] [t(15) = 1.58, p < 0.001] (63). Our study supports the finding of Mondino et al. (2016) which evaluated the effects of tDCS after 10 sessions. The AHRs scores of the active group significantly decreased from 27.2 (SD ± 4.1) to 19.1 (± 7.1), corresponding to a 28% (± 6) reduction (p < 0.01), whereas the decline in scores for sham participants between baseline and endpoint was non-significant (Mondino et al., 2016). Similar study by Bose et al. (2017) using the same study design as Brunelin et al. (2012), found significant positive effect of tDCS on auditory hallucination which was 30.22% (SD± 14.71) reduction in AHRs. Our study in contrast to the previous studies done by Fitzgerald et al. (2014), Smith et al. (2015) and Chang et al., (2018), that do not report significant effect of tDCS on auditory hallucinations in patients with schizophrenia.

Meta-analysis done by Yang, Fang, Tang et al., (2019) which included the study by Bose et al. (2017); Brunelin et al. (2012); Frohlich et al. (2016); and Mondino et al. (2016), showed that the mean AHRs reduction is 4.59 ± 1.16-95% C.I [2.7-9.1]. The variation in effects could be due to different protocols used, different duration of assessment of symptoms, different montages used for tDCS stimulation, and the difference in characteristics of patients in the study. The effect size in our study was smaller 1.47 ± 0.37 (95% C.I. 0.73 - 2.21) as compared to the above meta-analysis study by Yang et al., (2019).

Effect of tDCS on PANSS score-

In this study PANSS decreased from 65.66 ± 2.16 at baseline to 64.16 ± 2.16 on day 5 and then increased back to 65.22 ± 2.16 on day 30. Compared to AHRs, the response in PANSS is subdued, possibly as PANSS measures both domains - positive and negative symptoms.

In comparison to other studies such as, Gomes, Shiozawa, Dias et al. (2015) n = 24, stimulation used 2 mA, for 20 min, with electrodes size of 25 sq. cm, anode over the left DLPFC and cathode in the contra-lateral area that is on right DLPFC, found improvement in PANSS score. Similarly, Palm, Koester, Hasan, et al. (2016) n = 20, using 10 sessions of add-on active (2 mA, 20 min) or sham tDCS (anode: left DLPFC/F3; cathode: right supraorabil/F4), found significant benefit in PANSS at 2 weeks and follow-up period (Palm et al., 2016; Gomes et al., 2015), whereas Smith et al. (2015) n = 30, found no improvement in PANSS after 5 sessions of tDCS. In the study by Gomes, Trevizol, Ducos et al. (2018) (n = 24), both negative and positive symptoms improved contributing to overall PANSS improvement after 10 sessions of tDCS.

Effect of tDCS on Hallucinatory Behaviour (P3) of PANSS scale-

Our study showed improvement from 4.63 ± 0.15 to 4.16 ± 0.15 on P3 (Hallucinatory subscale of PANSS). Few studies have explored P3 component of PANSS as outcome variable for efficacy of PANSS. Smith et al. (2015) found improvement in P3 component of PANSS, while study done by Yoon, Kim, Lee et al. (2019) found that there were no statistically significant differences between the auditory hallucination symptoms before and after tDCS, despite the fact that there was a decrease in the hallucinatory behaviour subscale score of the PANSS.

Effect of tDCS on Negative symptoms:

In this study, there was minimal improvement in negative symptom domains of PANSS. On comparing with other studies, there have been conflicting results in context to negative symptoms in the literature. Recent studies by Brunelin et al. (2012), Gomes et al., (2015), Gomes et al., (2018) have shown an improvement in negative symptoms, whereas studies by Frohlich et al. (2016), Fitzgerald et al. (2014) and Shiozawa, da Silva, Cordeiro et al. (2013) showed no significant improvement.

In this study PANSS decreased from 27.2 (SD 5 ± 4.1) to 25.1 (± 7.7) [(d = 1.58, p < 0.001)](63). Our study supports the finding of Mondino et al. (2016) which compared to the above meta-analysis study by Yang et al., (2019).
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Effect of tDCS on insight-

The study did not lead to improvement in self-reflection, self-certainty and Beck’s composite insight scale. There have been few studies exploring effect of tDCS on insight in patients with schizophrenia. One study by Chang et al., (2018) which reported improvement in the level of insight into illness (effect size = 0.51, p < 0.001) and positive symptoms (effect size = 0.781, p < 0.001) by 5 days of tDCS compared to sham treatment. The beneficial effects on the two insight dimensions was sustained for one month after tDCS sessions (Chang et al., 2018). Another study on insight by Bose et al., (2014), showed that following tDCS sessions in schizophrenia (n = 21), there was a significant improvement in insight as assessed by Schedule for Assessment of Insight (SAI) score (baseline: 7.8 ± 4.4; follow-up: 12.2 ± 4.2; t = 4.0; p = 0.001).

Reason for lack of improvement in this study may be due to severity and chronic illness in the participants. There is loss of cortical brain matter in patients with chronic schizophrenia, include both grey and white matter, manifesting their greatest severity in the frontal lobe (Andreasop, Nopoulos, Magnotta et al.,2011), hence poorer result to brain stimulation for insight improvement.

The present study showed a significant reduction in auditory hallucinations after 10 sessions of tDCS. Unlike study by Fitzgerald et al., (2014), in which tDCS was applied once-daily for 15 days, showed no significant change in auditory hallucinations. In another study by Frohlich et al., (2016) that applied once-daily left fronto-temporo-parietal stimulation across 5 days showed no improvement in auditory hallucinations. Similarly, study by Smith et al., (2015), where once daily bi-frontal stimulation for 5-days was applied, showed no effect of tDCS on auditory hallucinations. The above studies suggest that the frequency of stimulation (i.e., twice-daily compared to once-daily) may be more efficacious, as most of the studies that reported a significant reduction in auditory hallucinations applied twice-daily tDCS resulting in adequate hyperpolarization at the cathode (Brunelin et al., 2012). Also, fronto-temporal placement of electrodes appears to produce positive results compared to other sites of placement (Kim, Iwata, Pittman et al., 2019).

We also found reduction in the P3 component of PANSS scale after tDCS sessions on day 5. However, the effect size was less as compared to improvement in AHRs scores. This may be because the item of hallucinations in the PANSS scale is less reliable to measure the severity of auditory hallucinations in a detailed manner. Whereas, the AHRs scale is an excellent tool for evaluating the hallucinatory symptoms (Van and de Beurs, 2007). Therefore, comprehensive assessment tools like AHRs are suggested in such studies, rather than using a single component such as P3.

This study reports significant negative correlation between improvement in AHRs and the illness duration of patients (rs = -0.49, p = 0.004) and also negative correlation between improvement in AHRs and the total baseline PANSS score of patients (rs = -0.69, p = 0.001) indicating that patients with longer illness duration and severity responded poorly to tDCS intervention. Such trend is also shown in pharmacological treatment, where chronic illness and the duration of untreated psychosis lead to poor response to antipsychotics (Carbon, Correll, 2014). The catecholaminergic hypertoncity results in continuos activation of hypothalamic, pituitary, adrenal axis, resulting in impaired neuroplasticity and permanent brain changes resulting in poor prognosis.

CONCLUSION

Transcranial direct current stimulation (tDCS) is a non-invasive neuromodulatory technique that is safe, portable and has been reported to be effective in patients with schizophrenia. The current study reports that add-on tDCS is effective in decreasing auditory hallucinations in patients with chronic schizophrenia, however, its effects were short lived. We suggest studying the possibility of maintenance tDCS for patients with chronic schizophrenia having refractory auditory hallucinations. This study and literature suggest a significant impact of electrical stimulation on auditory hallucinations in schizophrenia. A phase II randomized sham-controlled trial. Br J Psychiatry. 2015; 1: 989-91.

REFERENCES