PSYCHOLOGICAL MEDICINE

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

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ABSTRCT

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 are refractory to antipsychotic drugs. This causes significant distress and impairment in the quality of life of the affected persons (Shergill, Murray, McGuire, 1998). Inadequacy of pharmacotherapy, has led to a surge of interest in exploring newer treatment modalities like neuromodulation techniques. tDCS has been used in various studies to understand its effect on AVH (Smith, Boules, Mattiuz *et al*., 2015; Brunelin Mondino, Gassab *et al*., 2012; Frohlich, Burrello, Mellin *et al*., 2016; Mondino, Jardri, Suaud-Chagny *et al*.,2016; Chang, Tzeng, Chao *et al*., 2018; Bose, Shivakumar, Chhabra *et al*., 2017; and Fitzgerald, McQueen, Daskalakis *et al*., 2014).

tDCS is a non-invasive brain stimulation technique, where a weak direct current is used in the range of 0.5 to 2 mA, that is passed through the scalp by means of electrodes ranging in size, most commonly, from 25 to 35 sq. cm over designated areas of interest in an attempt to modulate the activity of specific brain regions (Paulus, 2011; Brunoni, Nitsche, Bolognini *et al*., 2012). tDCS modulates cortical resting potential and modifies the N-methyl-D-aspartate (NMDA) receptors, that results in neuroplasticity, however, other neurotransmitter like dopamine, serotonin, GABA, acetylcholine and adrenaline also play a pivotal role. (Nitsche, Lampe, Antal *et al*., 2006)

Earlier studies have shown that experiencing AVHs is linked with increased activity in fronto-temporal areas involved in speech generation and speech perception (Jardri, Pouchet, Pins *et al*., 2011). 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).

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*., (2014); Smith *et al*., (2015); Frohlich *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

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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 then after 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 undertaken 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 34.59 +- 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). The PANSS scores 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 slow (slower response and slower rise), possibly as PANSS measures both domains - positive and negative symptoms.

This study reports significant negative 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 (n = 30); Brunelin *et al*., 2012 (n = 30); Frohlich *et al*., 2016 (n = 26). We used the fronto-temporo-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 (TPJ). 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 TPJ 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 TPJ 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 27.2 (6.9) to 25.1 (7.7)] [(d = 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 5 ± 4.1) to 19.1 (± 7.1), corresponding to a 28% (± 26) 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 [1.27-7.91]. 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 contralateral area that is on right DLPFC, found improvement in PANSS score. Similarly, Palm, Keeser, 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 supraorbital/F4), found significant benefit in PANSS at 2 weeks and follow-up period (Palm *et al*., 2016; Gomes *et al*., 2015), while 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 PNSS 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.

Gomes *et al*., (2015), conducted a randomized, double-blind study. They applied anode over the left DLPFC, and cathode over the right DLPFC. A total of 15 patients with schizophrenia were randomized to either active group or the sham group. The active group received 20 min of tDCS once a day for 10 days and found reductions in negative symptom scores in PANSS.

In 2016, Palm and colleagues conducted a study including 20 patients with schizophrenia having predominately negative symptoms that were randomized to 10 sessions of active or sham tDCS with the anode at F3 and cathode at Fp2. Significant results were found at both primary outcomes i.e. score of Scale for the Assessment of Negative Symptoms (SANS) and secondary outcomes after 10 days i.e. PANSS score (Palm *et al*., 2016).

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 = 0.511, $p < 0.001$) 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 (Andreason, 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, Plitman *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 hyperactivity results in continuous 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 electrodes placement for a better outcome. Hence, we recommend exploring other locations of tDCS electrode placement and further optimizing the tDCS effect by more focalized stimulation using high definition tDCS with computational or neuroimaging guided target localization.

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