BRIEF RESEARCH COMMUNICATION

Transcranial direct current stimulation for refractory auditory hallucinations in schizophrenia: Acute and 16-week outcomes

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ABSTRACT

Background: Transcranial direct current stimulation (tDCS) has demonstrated efficacy against antipsychotic-refractory auditory verbal hallucinations (AVH) in schizophrenia. The duration of persistence of benefit is not well characterized.
Materials and Methods: Thirty-one adults with schizophrenia and medication-refractory AVH were treated with 2–3 mA tDCS in 30 min sessions, twice a day, 6 days a week, for 2–4 weeks. The anode was sited over F3 and the cathode midway between T3 and P3 in the 10–20 EEG system. Patients were assessed until a 4-month study endpoint using two auditory hallucination rating scales and the Positive and Negative Syndrome Scale (PANSS-N).
Results: Auditory hallucinations were moderately reduced by tDCS with 25%–29% improvement evident by the end of the 2nd week and another 10% improvement between week 2 and 4 months. There was no loss of benefit at the end of the 4-month study. There was also a small (11%) but statistically significant improvement in PANSS-N scores.
Conclusions: Although this study is limited by the nonblind, uncontrolled design, the results suggest that tDCS, as delivered, holds promise for treating refractory AVH in schizophrenia; the benefits persist beyond the short term.

Key words: Auditory, hallucinations, negative, refractory, schizophrenia, symptoms

INTRODUCTION

Despite advances in pharmacotherapy, disabling symptoms such as auditory verbal hallucinations (AVH) remain refractory to treatment in up to 30% of patients with schizophrenia. In this context, neurostimulation procedures such as repetitive transcranial magnetic stimulation (rTMS) have been shown to attenuate refractory AVH by modulating the abnormal temporoparietal cortical activity reported in neuroimaging studies.[1-4] Because similar changes can be induced by transcranial direct current stimulation (tDCS), this treatment has also been studied in schizophrenia patients with refractory AVH.[5]

tDCS administration results in prolonged hyperpolarization of the cerebral cortex under the cathode and prolonged increase in the resting membrane potential in the cortex under the anode. These effects reflect the cortical inhibition and excitation, respectively, that are described with low- and

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high-frequency rTMS.[6] As low-frequency rTMS delivered to the left temporoparietal junction has therapeutic action against refractory AVH,[7,8] it is possible that tDCS may have efficacy against AVH as rTMS does, but with greater convenience and a lesser expense. The evidence for the efficacy of tDCS in patients with antipsychotic-refractory AVH is based on carefully documented and instructive case reports and a small RCT.[9-15]

Because cathodal tDCS has effects similar to low-frequency rTMS,[16] tDCS may be a clinically viable alternative to rTMS for patients with refractory AVH. However, although benefits with tDCS have been described, little is known about the persistence of these benefits. This study was therefore planned with the following objectives:

1. To assess and confirm the efficacy of cathodal tDCS stimulation of the temporoparietal cortex in schizophrenia patients with refractory AVH
2. To assess the impact of anodal tDCS stimulation on negative symptoms in schizophrenia patients with refractory AVH
3. To assess the duration of persistence of these benefits, if any.

MATERIALS AND METHODS

Study design and site

This was an open, uncontrolled, single-arm, prospective study of the acute- and intermediate-term efficacy of tDCS in schizophrenia patients with antipsychotic-refractory AVH. The study was conducted in the Department of Psychiatry at IQRAA International Hospital and Research Center, Calicut. The study protocol was approved by the Institute Ethics Committee of IQRAA Hospital, and written informed consent was obtained from all patients.

Sample

The sample comprised 31 consecutive adult men and women, aged 18–65 years, with a clinical DSM-4 diagnosis of schizophrenia, all clinically right-handed individuals. All patients were required to have refractory AVH for at least the past 3 months, with refractory AVH defined as the daily presence of impairing AVH despite trials of at least two different antipsychotic medications at recommended doses for at least 1 month each. Of the patients, 20 were on clozapine, 7 were on olanzapine, 2 on quetiapine, and a sole patient on risperidone with all subjects in monotherapy. Doses of drugs were (mean [SD]) as follows: quetiapine, 450.0 (353.6); olanzapine, 14.3 (6.1); and clozapine 302.5 (126.6). The patient on risperidone was taking 8 mg/day. No patient had exposure to electroconvulsive therapy for the 6 months preceding the study. Patients were excluded if they had a concurrent alcohol or substance use disorder, or if they had a medical or psychiatric condition that could interfere with the understanding of or adherence to the tDCS treatment protocol.

Transcranial direct current stimulation administration

tDCS was administered through 25–35 cm^2 metal electrodes wrapped in saline-soaked gauze, using a device obtained from Zeebeetronics, Bengaluru, Karnataka, India. The anode was placed at F3, over the left dorsolateral prefrontal cortex (DLPFC), and the cathode was placed between T3 and P3, over the temporoparietal junction, based on the 10–20 electroencephalogram electrode positioning system. The electrodes were held firmly in position using an elastic hair band. A current intensity of approximately 2–3 mA was maintained all through the session. Each session lasted 30 min. Two sessions were scheduled each day, approximately 5–6 h apart. Sessions were conducted daily, 6 days a week for 2 consecutive weeks.

At the end of 2 weeks, patients were given an option to continue with tDCS if the benefit with treatment was insufficient. Ten patients opted to continue. Patients were continued on their existing antipsychotic regimen all through the study.

Assessments

Patients were assessed using the auditory hallucination rating scales (AHRS), AHRS1[3] and AHRS2,[17] and the Positive and Negative Syndrome Scale (PANSS).[18] Adverse events were assessed using the SAFTEE checklist for adverse effects.[19]

Assessments were conducted during the morning (before tDCS, if a session was scheduled) at baseline, at the end of 2 weeks, at the end of 4 weeks, and then at monthly intervals for the next 3 months. Thus, the total duration of the study was 4 months. Treatment and assessment were conducted by different study staff.

Statistical analysis

The intent-to-treat sample was defined as all patients who consented and received at least one session of tDCS. In the primary analysis, last-observation-carried-forward (LOCF) analysis of AHRS data was conducted using one-way repeated measures multivariate analysis of variance (RMANOVA). LOCF analysis, using the Friedman's test, was conducted for individual items on the AHRS scales. The relationship of age and sex with AHRS outcomes was examined using Pearson's correlation and Mann–Whitney tests. LOCF analysis of PANSS negative symptom scores was carried out using one-way RMANOVA. The significance threshold was set at $P < 0.05$.

RESULTS

Sample disposition

Thirty-one patients consented and were included in the study. The number of patients dropping out at the end of weeks 1, 2, 4, 8, 12, and 16 was 1, 0, 2, 8, 2, and 0, respectively. Thus, a total of 13 patients did not complete the 4-month study, and 18 patients provided complete data.

Sample description

The age of the sample ranged from 19 to 62 years. The M (SD) age was 35.8 (11.6) years. The sample consisted of 54.8% of males. Patients were educated for a M (SD) of 10.7 (3.4) years. Thirteen (41.9%) patients were married, 11 (35.5%) were living in a joint family, and 22 (71%) were unemployed. The M (SD) age at onset of illness was 24.2 (12.3) years.

Auditory hallucination rating scales outcomes

Last-observation-carried-forward analysis

The M (SD) total scale AHRS scores at different points in time are presented in Table 1. There was significant attenuation of scores for AHRS1 ($F = 8.31$, df = 6.25, $P < 0.001$) and AHRS2 ($F = 5.50$, df = 6.24, $P < 0.001$). For AHRS1, there was 29% reduction in the total score at the end of week 2 and a further 10% improvement thereafter; thus, at the end of 4 months, there was a total of 39% improvement. For AHRS2, there was 25% reduction in the total score by the end of week 2 and a further 9% improvement thereafter; thus, at the end of 4 months, there was a total of 34% improvement.

The M (SD) improvements in individual items of AHRS1 and AHRS2 are presented in Tables 2 and 3. As can be seen in Table 2, there was significant improvement in each item of AHRS1 with the bulk of the improvement apparent by the end of week 2. For AHRS2, improvements were apparent in each item except location, belief, and disruption; again, the bulk of the improvement was apparent by the end of week 2.

Remission was defined as AHRS total score = 0 and response rate was defined as >30% improvement. By the end of the 4 month study, on each AHRS scale, 5/31 (16.1%) patients had complete remission. By the end of the study, 16 (51.6%) patients had responded on AHRS1 and 14 (45.2%) had responded on AHRS2.

In exploratory analyses, there was no significant correlation between patient age and improvement on AHRS1 ($r = 0.06$) or AHRS2 ($r = -0.01$). The M (SD) improvement in AHRS1 was 11.7 (12.0) vs. 12.0 (7.8) in men vs. women, respectively (Mann–Whitney $z = 0.80$, $P = 0.43$). The M (SD) improvement in AHRS2 was 10.9 (12.0) vs. 9.2 (7.6) in men vs. women, respectively (Mann–Whitney $z = 0.10$, $P = 0.92$). Thus, no moderators of response were identified.

Table 1: Mean (standard deviation) auditory hallucination rating scale total scale scores using AHRS1 and AHRS2

	AHRS1 (*n*=31)	AHRS2 (*n*=31)
Baseline	30.3 (5.1)	30.3 (5.3)
Week 1	25.0 (9.6)	26.0 (9.5)
Week 2	21.5 (10.4)	22.7 (10.4)
Week 4	21.5 (9.6)	23.0 (10.2)
Week 8	20.8 (9.6)	22.7 (10.5)
Week 12	19.2 (9.8)	20.3 (10.7)
Week 16	18.5 (9.6)	20.0 (10.3)

Statistical inferences are presented in the text. AHRS – Auditory hallucination rating scale

Comparison of mean score of negative symptoms from baseline to 16th week shows very small (11%), but statistically significant improvement in PANSS-N score ($F = 4.25$, df = 6.2, $P = 0.005$).

Adverse effects

With the exception of occasional, mild, transient, intrasession tingling at the electrode site, no adverse effects were reported with tDCS. Tingling, if present, was managed by temporarily reducing current intensity.

DISCUSSION

There is limited literature on the use of tDCS to treat refractory AVH in schizophrenia. Many publications are case reports[9,10,20] and small sample size open clinical trials.[20] In a randomized, double-blind trial on schizophrenia patients with medication-refractory AVH, Brunelin *et al*. reported significant improvement with tDCS as compared with sham tDCS.[15] Bose *et al*. and Lindenmayer *et al*. in randomized, sham-controlled study reported beneficial effects of add-on tDCS to treat refractory AVH schizophrenia.[21,22]

In our open clinical trial, tDCS administered to the left temporoparietal junction ("inhibitory" cathodal tDCS) and to the left DLPFC ("excitatory" anodal tDCS) was found to moderately reduce the severity of refractory AVH and very slightly reduce negative symptoms in patients with schizophrenia. As early as after 2 weeks of treatment, we observed 25%–29% reduction in total AHRS scores. The effect of tDCS on hallucinations was maintained at a 4-month study endpoint, at which time about half of the sample was classified as responders, and 16% as remitters. The treatment gains at the study endpoint could not be attributed to medications because patients were maintained on the same medication regimen throughout the study period. The treatment was found to be safe and effective.

We acknowledge that, because we did not have a sham-treated control group, we cannot determine the extent to which a placebo response contributed to the treatment outcome. We suggest that double-blind, sham-controlled trials be conducted with long-term follow-up to quantify the magnitude and duration of tDCS-related benefits in refractory AVH symptoms in schizophrenia. Additional assessments could be useful, and these could range from evaluation of effects on quality of life and work performance to evaluation of changes on functional brain imaging.

CONCLUSIONS

Our results suggest that tDCS is an easy-to-use, low-cost stimulation tool with few side effects.[23-26] The treatment acts

Table 2: Mean (standard deviation) individual item scores in auditory hallucination rating scale 1

Items	Baseline	Week 1	Week 2	Week 4	Week 16	Friedman's test		
						χ^2	Df	*P*
Frequency	6.1 (2.9)	4.8 (3.1)	3.7 (3.0)	3.7 (3.0)	2.8 (2.7)	51.02	6	<0.001
Reality	4.8 (0.6)	4.3 (1.6)	4.0 (1.8)	4.0 (1.7)	3.6 (1.9)	12.37	6	<0.001
Loudness	2.8 (0.8)	2.3 (1.2)	2.0 (1.3)	2.1 (1.3)	1.9 (1.3)	14.36	6	0.03
Number of voices	4.4 (2.1)	3.6 (2.3)	3.4 (2.4)	3.3 (2.2)	2.9 (2.2)	14.74	6	0.022
Length	3.6 (1.0)	3.1 (1.5)	2.7 (1.6)	2.7 (1.6)	2.3 (1.6)	21.88	6	0.001
Attentional Salience	4.9 (1.5)	3.9 (2.0)	3.2 (1.9)	3.2 (1.9)	2.7 (1.9)	50.68	6	<0.001
Distress level	3.8 (1.1)	3.1 (1.4)	2.5 (1.4)	2.5 (1.4)	2.3 (1.4)	43.54	6	<0.001

Table 3: Mean (standard deviation) individual item scores in auditory hallucination rating scale 2

Items	Baseline	Week 1	Week 2	Week 4	Week 16	Friedman's test		
						χ^2	Df	*P*
Frequency	3.2 (0.9)	2.6 (1.3)	2.2 (1.3)	2.3 (1.2)	2.0 (2.2)	24.43	6	<0.001
Duration	2.7 (1.0)	2.2 (1.2)	1.9 (1.2)	1.9 (1.1)	2.5 (1.6)	18.63	6	<0.005
Location	2.9 (1.3)	2.7 (1.5)	2.5 (1.6)	1.7 (0.9)	1.4 (0.9)	3.74	6	0.71
Loudness	2.1 (0.8)	1.7 (1.0)	1.6 (1.0)	2.7 (1.4)	2.3 (1.5)	8.50	6	0.20
Beliefs about origin of voices	3.0 (1.1)	2.7 (1.3)	2.6 (1.4)	1.3 (1.5)	1.1 (1.4)	7.15	6	0.31
Amount of negative content of voices	2.1 (1.3)	1.7 (1.4)	1.4 (1.4)	1.4 (1.5)	1.1 (1.1)	16.54	6	0.01
Degree of negative content	2.3 (1.4)	1.9 (1.5)	1.5 (1.4)	2.2 (1.4)	2.0 (1.4)	17.74	6	0.01
Amount of distress	3.3 (1.6)	2.6 (1.3)	2.2 (1.4)	2.1 (1.4)	1.8 (1.4)	30.87	6	0.001
Intensity of distress	3.1 (1.2)	2.6 (1.3)	2.2 (1.3)	1.9 (1.1)	1.9 (1.1)	30.02	6	0.001
Disruption	2.1 (0.7)	2.0 (1.0)	1.9 (1.0)	2.9 (1.4)	1.8 (1.1)	1.01	6	0.99
Control	3.7 (0.7)	3.3 (1.2)	2.9 (1.5)	2.9 (1.4)	2.7 (1.5)	15.28	6	<0.02

on two distinct brain areas involved in the pathophysiology of schizophrenia. tDCS could constitute a new tool in the treatment of refractory symptoms. The feasibility of domiciliary tDCS treatment needs to be explored, with regular checks to ensure adherence to stimulation protocols.

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Conflicts of interest

There are no conflicts of interest.

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